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[Intervention Review]

Inhaled corticosteroids with combination inhaled long-acting beta₂-agonists and long-acting muscarinic antagonists for chronic obstructive pulmonary disease

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ABSTRACT

Background

Management of chronic obstructive pulmonary disease (COPD) commonly involves long-acting bronchodilators including beta-agonists (LABA) and muscarinic antagonists (LAMA). In individuals with persistent symptoms or frequent exacerbations, inhaled corticosteroids (ICS) are also used. LABA and LAMA bronchodilators are now available in single combination inhalers. However, the benefits and risks of adding ICS to combination LABA/LAMA inhalers remains unclear.

Objectives

To assess the effect of adding an inhaled corticosteroid (ICS) to combination long-acting beta₂-agonist (LABA)/long-acting muscarinic antagonist (LAMA) inhalers for the treatment of stable COPD.

Search methods

We carried out searches using the Cochrane Airways Group Specialised Register of Trials (searched 20 September 2016), Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 12) in the Cochrane Library (searched 15 December 2015) and MEDLINE (searched 15 December 2015). We also searched ClinicalTrials.gov, World Health Organisation (WHO) trials portal and pharmaceutical company clinical trials' databases up to 7 January 2016.

Selection criteria

We included parallel-group, randomised controlled trials (RCTs) of three weeks' duration or longer which compared treatment of stable COPD with ICS in addition to combination LABA/LAMA inhalers against combination LABA/LAMA inhalers alone.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

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Main results

We identified a total of 586 records in our search. Following removal of duplicates, 386 abstracts were assessed for inclusion. Six studies were identified as potentially relevant; however, all failed to meet the inclusion criteria on full-text assessment or after contacting the corresponding author to clarify study characteristics.

Authors' conclusions

There are currently no studies published assessing the effect of ICS in addition to combination LABA/LAMA inhalers for the treatment of stable COPD. As combination LABA/LAMA inhalers are now widely available, there is a need for well-designed RCTs to investigate whether ICS provides any added therapeutic benefit.

PLAIN LANGUAGE SUMMARY

In stable COPD, should inhaled corticosteroids be used with combination long-acting beta₂-agonist/long-acting muscarinic antagonist inhalers?

Why is this question important?

Chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema, is a common long-term lung disease often associated with smoking. Patients with COPD experience persistent symptoms including breathlessness, cough and phlegm production. COPD is commonly treated with a number of inhaled medications. These include long-acting bronchodilators (LABA and LAMA) that open (dilate) the airways; and inhaled corticosteroids (ICS), which are medications that suppress inflammation in the airways. In some individuals with particularly persistent symptoms or frequent exacerbations (episodes where their symptoms become worse), all three classes of these inhaled medications are used.

LABA and LAMA bronchodilators are now available in single combination inhalers. These combination inhalers have been found to improve adherence and patient outcomes. Presently, it is unclear whether using an ICS in addition to these new combination LABA/LAMA inhalers provides any additional therapeutic benefit or risk of side-effects.

How did we answer this question?

We looked for all studies which compared treatment of stable COPD with ICS in addition to combination LABA/LAMA inhalers against combination LABA/LAMA inhalers alone. This process involved a detailed search of multiple electronic databases for trials up to 9 December 2015.

What did we find?

Our review did not identify any studies assessing the relative benefits and risks of these two treatment strategies.

Conclusion

No relevant trials have been published to date. We cannot confirm any benefit from this review of adding ICS to a combination LABA/LAMA inhaler for the treatment of stable COPD.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a common respiratory condition associated with substantial morbidity and mortality (GOLD 2016). It is currently the fourth leading cause of death worldwide (WHO 2012). In the Burden of Obstructive Lung Disease (BOLD) initiative, a large international study of

COPD, the prevalence of stage II or higher COPD was reported to be 10.1% using the Global Initiative for Obstructive Lung Disease (GOLD) definition of disease (Buist 2007; GOLD 2016).

The most common cause of COPD is tobacco smoke exposure. However, occupational dusts and air pollution have been identified as strong independent risk factors (GOLD 2016). Airway inflammation in COPD, caused by inhalation of noxious agents, causes small airways disease and parenchymal destruction. These changes impair expiratory flow and result in both resting and dynamic hyperinflation of the lungs (Bateman 2014). The characteristic symptoms of COPD include persistent breathlessness, cough and sputum production, all of which are usually progressive in nature.

The natural progression of COPD is characterised by episodes of clinical deterioration, termed exacerbations, which involve both increased airway and systemic inflammation (Wedzicha 2013). COPD exacerbations are associated with an increased risk of mortality, poorer quality of life, and long-term decline in lung function (Rennard 2004; Wang 2005). These effects are greater in those who experience frequent exacerbations (Vestbo 2011; Halpin 2012). Pharmacological treatment of COPD is therefore aimed at relieving symptoms, improving quality of life and preventing exacerbations (GOLD 2016).

Description of the intervention

Bronchodilators are a key aspect of the pharmacological management of COPD, usually following a stepwise approach in which short-acting agents are used initially to control symptoms (NICE 2010; COPDX 2016; GOLD 2016). In individuals with persistent symptoms, combined bronchodilators of different classes are recommended to maximise bronchodilation. Inhaled long-acting

beta₂-agonists (LABA) and long-acting muscarinic antagonists (LAMA) are most commonly used.

The mechanism of bronchodilation by LABA and LAMA agents is achieved by different pathways. Beta₂-agonists stimulate adenylyl cyclase activity and directly cause smooth muscle relaxation while muscarinic antagonists inhibit the action of acetylcholine on airway muscarinic (M₃) receptors and indirectly cause smooth muscle relaxation (de Miguel-Díez 2014). Drugs in both classes of bronchodilator, LABA and LAMA, are beneficial for quality of life and lung function in COPD both individually and when given together (Kew 2014a).

Although LABA and LAMA agents have conventionally been administered via separate inhalers, new combination inhalers have been developed. These combination inhalers may promote adherence and improve patient-centred outcomes (van der Molen 2012). Moreover, combined LABA/LAMA inhalers have demonstrated superior efficacy compared to the individual components, with similar safety profiles (Rodrigo 2014; Farne 2015). Current combinations include:

- Aclidinium/Formoterol;
- Glycopyrronium/Indacaterol;
- Umeclidinium/Vilanterol; and
- Tiotropium/Olodaterol.

GOLD guidelines recommend triple therapy with inhaled corticosteroids (ICS), LABA and LAMA in patients with persistent symptoms and a high risk of exacerbations (Group D) who are unresponsive to ICS/LABA or LAMA therapy alone (GOLD 2016). In contrast, UK guidelines recommend the addition of LAMA in individuals who remain breathless or have exacerbations despite taking LABA/ICS, irrespective of their forced expiratory volume

in one second (FEV₁) (NICE 2010).

Evidence on the efficacy of triple therapy compared to dual bronchodilator therapy is, however, limited to a small number of clinical trials (Gaebel 2011). Findings from the WISDOM (Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD) trial suggest that the beneficial effect of ICS therapy may be limited to achieving an initial phase of clinical stability in patients with stable COPD. However, the long-term role of ICS therapy in COPD management remains unclear (Magnussen 2014). Little is known specifically about the efficacy of ICS used in addition to new combination LABA/LAMA inhalers. This topic will be the focus of this review.

How the intervention might work

As individual classes of treatment in COPD, LABA and LAMA are effective in improving health-related quality of life, improving lung function outcomes (Geake 2015), and reducing exacerbations (Kew 2013). A slightly larger improvement in health-related quality of life and lung function is seen when Tiotropium (LAMA) is added to a LABA, compared with either agent alone (Karner 2012; Farne 2015). A network meta-analysis of treatment options specifically for patients with severe COPD (FEV predicted 40% to 50%) who required additional treatment to short-acting bronchodilators, found that combination ICS/LABA was the highest ranked intervention for improving quality of life compared to placebo at six and 12 months (Kew 2014a). LAMA and LABA therapy were independently ranked second and third, and ICS alone was ranked fourth at six months, although class differences between LABA, LAMA and ICS were less prominent at 12 months.

ICS are anti-inflammatory drugs that in COPD reduce the rate of exacerbation and improve quality of life, although they do not have a significant effect on overall mortality or on the overall long-term decline in FEV (Yang 2012). Responsiveness to ICS varies (Miravittles 2011). It may be related to an eosinophilic inflammatory profile (Siva 2007; Miravittles 2011), an obstructive-dominant rather than an emphysema-dominant phenotype (Lee 2009), and may be predicted by a bronchial hyperresponsiveness (BHR) (Leuppi 2005), or by elevated levels of exhaled nitric oxide

(Kunisaki 2008). In contrast, ICS delivered alone or in combination with a LABA is associated with an increased risk of pneumonia, although no increase in mortality has been reported (Spencer 2011; Kew 2014b). There is currently insufficient evidence to confirm any benefit of adding ICS to LABA or LAMA in COPD (Karner 2011).

Why it is important to do this review

The best combination of therapeutic agents for the treatment of COPD has yet to be established. A review to assess the recently introduced combination LABA/LAMA inhalers against placebo, and their individual components is in preparation (Sarai 2014). However, the effect of adding regular ICS to combination LABA/LAMA inhalers for treatment of COPD is not yet known, and this is the focus of this review.

OBJECTIVES

To assess the effect of adding an inhaled corticosteroid (ICS) to combination long-acting beta₂-agonist (LABA)/long-acting muscarinic antagonist (LAMA) inhalers for the treatment of stable COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel-group randomised controlled trials (RCTs) that were reported as full-text articles, abstract only, or as unpublished data. We excluded studies of less than three weeks' duration due to the expected delayed onset of ICS activity.

Types of participants

We included all participants with a diagnosis of stable COPD and recorded the study authors' definition of stable COPD. We did not exclude participants with significant co-morbidities.

Types of interventions

We included studies comparing combination LABA/LAMA inhalers plus an ICS versus combination LABA/LAMA combination inhalers without an ICS (with or without placebo control).

Types of outcome measures

Primary outcomes

1. **Acute exacerbation of COPD (AECOPD):** defined as needing treatment with oral steroids, antibiotics or hospital attendance for a COPD exacerbation, or a combination of these treatments. Exacerbation events based on standardised patient-reported outcome tools for measuring changes in symptoms were also accepted.
2. **Respiratory health-related quality of life (HRQoL):** measured by the Chronic Respiratory Questionnaire (CRQ) or St. George's Respiratory Questionnaire (SGRQ).
3. **Pneumonia and other serious adverse events:** defined as requiring treatment or hospital admission for pneumonia or other serious adverse events.

Secondary outcomes

- **Symptom score:** measures of breathlessness, cough, wheeze and sputum production, preferably using validated scales.
- **Lung function:** pre-bronchodilator (BD) and post-BD measure including FEV and FVC.
- **Physical capacity:** measures including timed walking tests, endurance tests.
- **Mortality**

Reporting one or more of the outcomes listed here was not an inclusion criterion for studies in this review.

Search methods for identification of studies

Electronic searches

We identified studies from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Information Specialist for the Group. The Register 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, and through handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). We searched all records in the CAGR using the search strategy presented in Appendix 2 up to 20 September 2016. We also searched CENTRAL and MEDLINE, limited to the previous 24 months, for additional studies (see Appendix 3 for further details) on 15 December 2015. We imposed no restriction on the language of publication.

Searching other resources

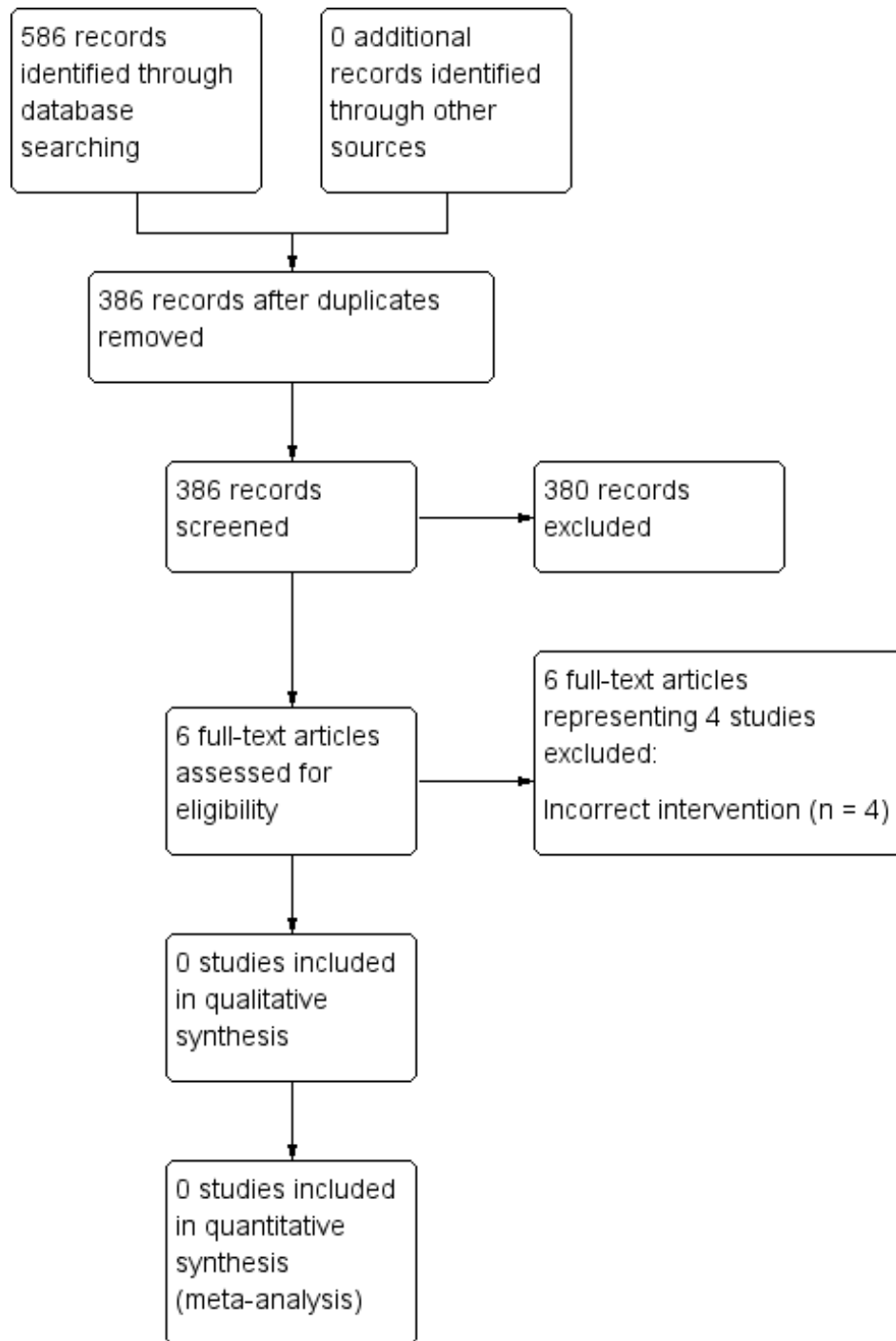
We screened the reference lists of all primary studies and review articles for additional references. We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov), the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) and clinical trial databases of pharmaceutical companies manufacturing combination LAMA/LABA inhalers (GSK, Novartis, Boehringer Ingelheim, AstraZeneca, Forest Laboratories) up to 7 January 2016.

Data collection and analysis

Selection of studies

Two review authors (DT, CW) independently screened the titles and abstracts of all records identified as a result of the search. Eligible or potentially eligible records were retrieved in full-text and independently screened by two review authors (DT, CW) to identify studies for inclusion and record reasons for exclusion of ineligible studies. Disagreements were resolved through discussion; or, if required, in consultation with a third review author (JW). We identified and excluded duplicates and collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We recorded the selection process as a PRISMA flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram



Data extraction and management

Two review authors (DT, CW) planned to independently extract outcome data from the included studies using a data collection form. Data for extraction included the following:

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 condition, 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 specified and collected and time points reported;

5. **Other:** funding for study and notable conflicts of interest of study authors.

When disagreements occurred, a third review author (JW) would arbitrate. We planned for one review author (DT) to transfer data into Review Manager 5 (RevMan 2014), which were then to be double checked by a second review author (CW) for accuracy.

Assessment of risk of bias in included studies

Two review authors (DT, CW) planned to independently review and assess risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to discuss areas of disagreement with a third review author (JW). Criteria for assessing risk of bias included:

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other biases.

We planned to grade each potential source of bias as 'high', 'low' or 'unclear' and to provide a quote from the study report along with a justification for our judgement in a 'Risk of bias' table. We planned to summarize the risk of bias judgements across different studies for each domain listed.

Measures of treatment effect

We expected to encounter both dichotomous and continuous data. We planned to analyse dichotomous data as odds ratios (OR), continuous data as mean differences (MD) or standardised mean differences (SMD), and narratively describe skewed data reported

as medians and interquartile ranges. We also planned to undertake meta-analyses only of studies with sufficient similarity (e.g. treatments, participants, clinical question) to derive meaningful pooled estimates. Where multiple trial arms were reported in a single trial, we would only include relevant arms. Where two comparisons (e.g. drug A versus placebo and drug B versus placebo) were combined in the same meta-analysis, we planned to halve the control group to avoid double-counting.

Unit of analysis issues

We planned to use participants, rather than events, as the unit of analysis to avoid counting participants more than once.

Dealing with missing data

We contacted investigators to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was identified as an abstract only). If these were not available, and the study authors did not report the true intention-to-treat (ITT) data, we intended to perform an available case analysis by including data for all participants for whom data were collected (whether or not participants completed the trial) and sensitivity analyses to explore the impact of including such studies in the overall assessment of results.

Assessment of heterogeneity

We planned to use the I^2 statistic to measure heterogeneity among the studies in each analysis. If we identified substantial heterogeneity (< 39% unimportant, 40% to 60% moderate, 60% to 100% substantial), we planned to report this and explore possible causes by subgroup analysis.

Assessment of reporting biases

We planned to create standard funnel plots to explore possible small-study and publication biases if we pooled more than 10 studies. We planned to assess reporting bias according to the *Cochrane Handbook for Systematic Reviews of Interventions* and grade potential sources as high, moderate or low risk (Higgins 2011).

Data synthesis

In the absence of significant heterogeneity, we planned to combine study results using a fixed-effect model. Where heterogeneity was significant ($I^2 > 40%$) we planned to perform a sensitivity analysis using a random-effects model.

Subgroup analysis and investigation of heterogeneity

We intended to explore potential causes of heterogeneity by performing the following subgroup analyses:

- Different LAMA/LABA combinations.
- Baseline COPD severity (severe to very severe versus mixed population).
- Blood or sputum eosinophilia (eosinophilia versus no eosinophilia).
- Length of follow-up (less than six months versus six months or longer).
- Baseline ICS use (participants with baseline ICS use versus participants without baseline ICS use).

Sensitivity analysis

We intended to carry out the following sensitivity analyses.

- A comparison based on our risk of bias assessments.
- A comparison of available case analyses versus true ITT analyses, when the ITT analyses are imputed with best-case and worse-case outcome data.
- A comparison of results from fixed-effect models versus results from random-effects models.

RESULTS

Description of studies

Results of the search

We identified a total of 586 records in our search (Figure 1). After removal of duplicates, 386 abstracts were assessed for inclusion. Six records, arising from four studies, were identified as potentially relevant. All failed to meet the inclusion criteria on full-text assessment or after contacting the corresponding authors to clarify study characteristics (see: [Characteristics of excluded studies](#)).

No on-going trials were identified in the search of ClinicalTrials.gov (www.ClinicalTrials.gov), the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) or clinical trial databases of pharmaceutical companies manufacturing combination LAMA/LABA inhalers.

Included studies

No studies met the inclusion criteria for this review.

Excluded studies

A total of four studies (six full-text articles) were excluded ([Böyükbas 2011](#); [Hara 2007](#); [James 2013](#); [Magnussen 2014](#)). The reason for exclusion for all four studies was incorrect intervention.

Risk of bias in included studies

Not applicable.

Allocation

Not applicable.

Blinding

Not applicable.

Incomplete outcome data

Not applicable.

Selective reporting

Not applicable.

Other potential sources of bias

Not applicable.

Effects of interventions

Not applicable.

DISCUSSION

Summary of main results

This systematic review did not identify any on-going or completed randomised controlled trials comparing the treatment of stable COPD with ICS plus combination LABA/LAMA inhalers against combination LABA/LAMA inhalers alone.

Overall completeness and applicability of evidence

Not applicable.

Quality of the evidence

Not applicable.

Potential biases in the review process

Not applicable.

Agreements and disagreements with other studies or reviews

Combination LABA/LAMA inhalers are now widely available and have demonstrated improvements in lung function and symptom score when compared to placebo or the components individually (Rodrigo 2014). There is strong evidence to support the role of regular ICS therapy in some COPD patients, particularly those with severe to very severe disease and those at a high risk of exacerbations (Calverley 2007; GOLD 2016). Existing evidence suggests that ICS therapy in COPD reduces rates of exacerbation, reduces the rate of decline in quality of life, and possibly reduces the rate of decline in lung function (Yang 2012). ICS therapy, however, is also associated with increased risk of oropharyngeal candidiasis and pneumonia (Kew 2014b; Yang 2012). The specific risk versus benefit profile of adding ICS to new combination LABA/LAMA inhalers remains unclear.

There is some evidence that stepwise withdrawal of ICS after achieving a period of clinical stability may be non-inferior to long-term triple therapy in respect to exacerbation frequency in patients with severe but stable COPD (Magnussen 2014). In contrast, abrupt withdrawal of ICS has been associated with increased exacerbation frequency and reduced health-related quality of life (van der Valk 2002). Evidence from these studies should be considered when determining the optimal role of ICS added to combination LABA/LAMA inhalers.

AUTHORS' CONCLUSIONS

Implications for practice

No relevant randomised controlled trials have been published to date. We cannot confirm any benefit from this review for the addition of ICS to a combination LABA/LAMA inhaler for the treatment of stable COPD.

Implications for research

There is a need for well-designed randomised controlled trials to investigate whether addition of ICS to combination LABA/LAMA inhalers provides any therapeutic benefit.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bölükbas 2011	Incorrect Intervention: comparison of LAMA + LABA/ICS versus LAMA + LABA (separate inhalers)
Hara 2007	Incorrect Intervention: comparison of LAMA versus LABA/ICS
James 2013	Incorrect Intervention: comparison of LABA + LAMA (separate inhalers) versus LABA + LAMA + ICS (separate inhalers). Corresponding author contacted - the authors were blinded to the specific inhalers used. They were unable to provide further details
Magnussen 2014	Incorrect Intervention: WISDOM study - comparison of LABA + LAMA + ICS (separate inhalers) versus LABA + LAMA + stepwise withdrawal of ICS (separate inhalers)

DATA AND ANALYSES

This review has no analyses.

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
CENTRAL (<i>The Cochrane Library</i>)	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 Respiriology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards

(Continued)

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. (randomised 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. CAGR search strategy

#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):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 LAMA
#8 MeSH DESCRIPTOR Muscarinic Antagonists
#9 tiotropium
#10 aclidinium
#11 glycopyrronium
#12 umeclidinium
#13 darotropium OR GSK233705
#14 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15 LABA
#16 MeSH DESCRIPTOR Adrenergic beta-2 Receptor Agonists
#17 salmeterol
#18 formoterol
#19 bambuterol
#20 vilanterol
#21 indacaterol
#22 olodaterol
#23 carmoterol
#24 abediterol OR LAS100977
#25 PF-610355
#26 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
#27 QVA149
#28 (#14 and #26) OR #27
#29 ICS:TI,AB
#30 inhal* NEAR2 (corticosteroid* or steroid*)
#31 fluticasone
#32 budesonide
#33 beclomethasone
#34 triamcinolone
#35 flunisolide
#36 #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
#37 #6 AND #28 AND #36

Appendix 3. CENTRAL, MEDLINE (PubMed) and Embase search strategies

CENTRAL

#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):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 LAMA
#8 MeSH DESCRIPTOR Muscarinic Antagonists

Inhaled corticosteroids with combination inhaled long-acting beta₂-agonists and long-acting muscarinic antagonists for chronic obstructive pulmonary disease (Review)

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#9 tiotropium
 #10 aclidinium
 #11 glycopyrronium
 #12 umeclidinium
 #13 darotropium OR GSK233705
 #14 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
 #15 LABA
 #16 MeSH DESCRIPTOR Adrenergic beta-2 Receptor Agonists
 #17 salmeterol
 #18 formoterol
 #19 bambuterol
 #20 vilanterol
 #21 indacaterol
 #22 olodaterol
 #23 carmoterol
 #24 abediterol OR LAS100977
 #25 PF-610355
 #26 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
 #27 QVA149
 #28 (#14 and #26) OR #27
 #29 ICS:TI,AB
 #30 inhal* NEAR2 (corticosteroid* or steroid*)
 #31 fluticasone
 #32 budesonide
 #33 beclomethasone
 #34 triamcinolone
 #35 flunisolide
 #36 #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
 #37 #6 AND #28 AND #36

MEDLINE

#1 COPD[MeSH Terms]
 #2 LAMA
 #3 (long-acting OR "long acting") AND "Muscarinic Antagonists"[Mesh]
 #4 tiotropium
 #5 aclidinium
 #6 glycopyrronium
 #7 umeclidinium
 #8 darotropium OR GSK233705
 #9 (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
 #10 LABA
 #11 (long-acting OR "long acting") AND "Adrenergic beta-2 Receptor Agonists"[Mesh]
 #12 salmeterol
 #13 formoterol
 #14 bambuterol
 #15 vilanterol
 #16 indacaterol
 #17 olodaterol
 #18 carmoterol
 #19 abediterol OR LAS100977
 #20 PF-610355
 #21 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)

#22 QVA149
 #23 (#9 AND #21) OR #22
 #24 ICS
 #25 “inhaled corticosteroid*” OR “inhaled steroid*”
 #26 fluticasone
 #27 budesonide
 #28 beclomethasone
 #29 triamcinolone
 #30 flunisolide
 #31 (#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30)
 #32 randomised controlled trial [pt]
 #33 controlled clinical trial [pt]
 #34 randomised [tiab]
 #35 placebo [tiab]
 #36 clinical trials as topic [mesh: noexp]
 #37 randomly [tiab]
 #38 trial [ti]
 #39 (#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38)
 #40 (animals [mh] NOT humans [mh])
 #41 (#1 AND #23 AND #31 AND #39) NOT #36
 #42 #41 AND (“2014/01/01”[Date - Publication] : “3000”[Date - Publication])

Embase

#1 exp chronic obstructive lung disease/
 #2 LAMA.mp.
 #3 (long-acting) AND (exp muscarinic receptor blocking agent/)
 #4 exp tiotropium bromide/
 #5 exp aclidinium bromide/
 #6 exp glycopyrronium bromide/
 #7 exp umeclidinium/
 #8 exp darotroprrium bromide/
 #9 2 or 3 or 4 or 5 or 6 or 7 or 8
 #10 LABA.mp.
 #11 (long-acting) AND (exp beta 2 adrenergic receptor stimulating agent/)
 #12 exp salmeterol/
 #13 exp formoterol/
 #14 exp bambuterol/
 #15 exp vilanterol/
 #16 exp indacaterol/
 #17 exp olodaterol/
 #18 exp carmoterol/
 #19 exp abediterol/
 #20 exp pf 610355/
 #21 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
 #22 exp glycopyrronium bromide plus indacaterol/
 #23 (9 and 21) or 22
 #24 ICS.mp.
 #25 inhaled corticosteroid*.mp. or inhaled steroid*.mp.
 #26 exp fluticasone/
 #27 exp budesonide/
 #28 exp beclometasone/
 #29 exp triamcinolone/

#30 exp flunisolide/

#31 24 or 25 or 26 or 27 or 28 or 29 or 30

#32 1 and 23 and 31

#33 limit 32 to (human and (randomised controlled trial or controlled clinical trial) and yr="2014 -Current")

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