

Comparative safety and effectiveness of inhaled long-acting agents (corticosteroids, beta agonists, anticholinergics) for chronic obstructive pulmonary disease

Comprehensive Research Plan: Systematic Review Unit

April 4th, 2014

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Background

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation in the lungs [1]. COPD is commonly assessed by clinical examination and spirometry. Important indicators considered in the diagnosis of COPD include age over 40 years and any of the following: 1) progressive and persistent dyspnea that worsens with exercise, 2) chronic cough, 3) chronic sputum production, 4) history of exposure to smoke from tobacco or cooking, occupational dusts and chemicals, and 5) family history of COPD [1].

COPD causes significant burden of illness, reduced quality of life, and premature death [2]. Symptoms include chronic cough, sputum production, and dyspnea [3]. The global prevalence of COPD has been estimated at 7.6% using data from a systematic review including 28 countries [4]. However, this is likely a conservative estimate, due to under-reporting and under-diagnosis. The prevalence and burden of COPD is rising due the greater proportion of elderly people in the population [1]. It is estimated that COPD will be the third-leading cause of death by 2020 [5].

The treatment of COPD usually involves reducing exposure (e.g., smoking cessation, occupation modifications), increasing exercise, and implementing appropriate pharmacologic therapy [1]. The most common drug classes are beta₂-agonists, anticholinergics, and methylxanthines. Inhaled corticosteroids (ICS) and systemic corticosteroids are often useful for acute exacerbations. The mode of administration may include inhaler, nebulizer, oral, or injection, depending on the type of medication.

According to the Global Initiative for COPD (GOLD), inhaled bronchodilators are recommended for patients with stable COPD [1]. Long-acting agents are preferred over short-acting agents [1]. ICS are recommended for those with severe airflow restrictions or who are experiencing frequent exacerbations. For these patients, combination therapy is recommended instead of increasing the dosage of the current therapy, as it might be more effective and safer [1].

There are at least 9 Cochrane reviews that have examined the above agents for COPD. These include the following: 1) combination ICS and long-acting beta₂-agonist (LABA) versus tiotropium (a long-acting anticholinergic [LAMA]) [6], 2) combination ICS and LABA and LAMA versus LAMA alone or ICS and LABA [7], 3) combined ICS and LABA in one inhaler versus LABA alone [8], 4) combined ICS and LABA in one inhaler versus ICS alone [9], 5) combined ICS and LABA in one inhaler versus placebo [10], 6) LABA plus tiotropium versus tiotropium or a LABA alone [11], 7) tiotropium versus LABA [12], 8) tiotropium versus placebo [13], and 9) tiotropium plus ICS plus LABA versus tiotropium plus LABA [14]. In the combination ICS and LABA versus tiotropium review, only 3 randomized clinical trials (RCTs) involving 1,528 patients were included after searching until November 2012 [6]. A meta-analysis was not conducted but the results from one RCT suggested that there were significantly more deaths for tiotropium alone (however this was affected by a high drop-out rate in the ICS and LABA combined group); more hospitalizations and pneumonia were observed in the fluticasone/salmeterol group [6]. There were no significant differences in hospitalizations due to exacerbation or exacerbations overall [6]. In the combination ICS and LABA and LAMA versus LAMA alone or combination ICS and LABA review, 3 RCTs were included (with 1,021 patients) [7]. There

were no statistically significant differences in mortality, hospitalizations, and episodes of pneumonia or adverse events [7]. Combination therapy plus tiotropium was superior regarding quality of life, lung function, and forced expiratory volume. Meta-analysis was not conducted on exacerbations, due to significant heterogeneity [7]. In the review comparing combined ICS and LABA versus LABA alone, 14 RCTs were included (with 11,794 patients) after searching the literature until November 2011 [8]. The authors found that patients receiving ICS and LABA had higher quality of life, fewer exacerbations and less mortality compared with LABA alone [8]. However, there were more cases of pneumonia for combination ICS and LABA versus LABA alone. No significant differences were observed in hospitalizations [8]. In the review comparing ICS and LABA versus ICS alone, 15 RCTs were included (with 7,814 patients) after searching the literature until June 2013 [9]. The authors noted significantly fewer exacerbations for combination ICS and LABA versus ICS alone, yet there were no significant differences in hospitalizations or adverse events [9]. Finally, in the review comparing ICS and LABA versus placebo, 19 RCTs (with 10,400 patients) were included after searching the literature until June 2013 [10]. Combined therapy reduced exacerbations, mortality, symptoms, and increased health status and lung function [10]. However, combined therapy was associated with more pneumonia compared with placebo.

Karner and colleagues searched for literature until January 2012 in their review of LABA plus tiotropium versus tiotropium or a LABA alone [11]. The authors included 5 RCTs and they found that LABA plus tiotropium resulted in improved quality of life compared with tiotropium alone; they found no differences in mortality or hospitalizations [11]. In the review of tiotropium versus LABA, 7 RCTs and 12,223 patients were included [12]. The authors found that little to no differences were observed between these agents for all outcomes, except that there were fewer serious adverse events and study drop-outs for tiotropium versus LABA. Twenty-two RCTs and 23,309 patients were included in the review of tiotropium versus placebo [13]. The authors found that tiotropium improved quality of life and reduced exacerbations versus placebo. Finally, Karner and colleagues searched until February 2011 for their review of tiotropium plus ICS plus LABA versus tiotropium plus LABA [14]. Only one trial was included and the authors were unable to make definitive conclusions regarding these treatment comparisons.

It's important to note that there is a planned Cochrane review that will focus on long-acting inhaled therapy (including LABA, anticholinergics, and ICS) for COPD [15]. The authors have published their protocol and are planning to do a network meta-analysis on this topic. However, we have no idea when these results will be made available as the protocol was only published earlier this year.

In addition to the planned Cochrane review including a network meta-analysis [15], there have been a number of published network meta-analyses examining pharmacotherapy for COPD. Four of these will be described briefly here. Forty RCTs were included in a network meta-analysis examining all long-acting bronchodilators [16]. The literature was searched until July 2011. The authors concluded that indacaterol, glycopyrronium, and tiotropium were likely the most effective bronchodilators [16]. In a network meta-analysis of all long-acting muscarinic agents (LAMA), 21 studies were included (with 22,542 patients) after searching the literature until October 2012 [17]. It was found that the newest LAMA treatment (aclidinium) was likely similar to pre-existing agents (tiotropium and glycopyrronium) regarding lung function, quality of life, and dyspnea [17]. Another network meta-analysis of inhaled drugs for COPD included 35 RCTs (with 26,786 patients) after searching the

literature until November 2007 [18]. The authors concluded that ICS and LABA combination therapy reduced exacerbations only in patients with low forced expiratory volume [18]. Finally, one network meta-analysis was funded by private industry (Merck, Dhome, and Nycomed) and examined RCTs greater than 24 weeks duration evaluating the effects of LABA (formoterol or salmeterol), LAMA (tiotropium), ICS (fluticasone or budesonide), PDE4 inhibitors (roflumilast), and combinations of these interventions [19]. The authors included 26 RCTs after searching the literature until 2010. They concluded that combination therapy is likely superior to single therapy regarding exacerbations [19].

In summary, evidence from previous reviews suggests that combination therapy is promising for patients with COPD. However, it is unclear which combinations are the most optimal or whether combination therapy is associated with more harm compared with single therapy. In order to examine this further, we are proposing to conduct a systematic review and network meta-analysis. Although previous network meta-analyses exist on this topic, none are up-to-date and none includes all of the agents of interest. For example, although one network meta-analysis examined LAMA, LABA, and ICS, it was **funded by private industry** and the authors restricted it to RCTs > 24 weeks duration and specific types of agents (i.e., **it was not a drug class systematic review**) [19].

Objective

To examine the comparative safety and efficacy of long-acting inhaled agents (ICS, LABA, LAMA) for patients with COPD.

Study Questions:

- 1) What is the comparative safety and efficacy of inhaled LAMAs (alone or in combination) versus ICS, inhaled LABA, and placebo [in any combination] for adults with COPD?
- 2) Which intervention (or combination) is the most effective and safe for adults with COPD?

PICO Statement

The population, intervention, comparator, and outcome (PICO) statement, including the study designs of interest, is as follows.

Study Population:

Adults with COPD. We will report the way that COPD was diagnosed across the included RCTs and conduct a sub-group analysis on this (please see the synthesis section below for further details). We will also consider sub-group analysis by severity of COPD, gender, and age (e.g., ≥ 65 years of age). Since the GOLD criteria have changed over time, a clinician (SES) will review all of the included studies to establish the COPD severity using the most recent GOLD guidelines.

Intervention:

Inclusion: inhaled LABA (e.g., formoterol, indacaterol, salmeterol, other LABAs), ICS (e.g.,

beclomethasone, budesonide, fluticasone, mometasone, other ICSs), LAMA (e.g., acclidinium bromide, glycopyrronium bromide, tiotropium, other LAMAs), and their combinations in one inhaler (e.g., LABA and ICS: formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone, vilanterol/fluticasone). We will focus on dosages/devices approved for use in Canada. For example, we will not include Spiriva Respimat (5 mcg tiotropium) because it is not approved in Canada.

Exclusion: LABA (nebulizer and transdermal, e.g., arformoterol, tulobuterol, bambuterol), ICS (nebulizer), short-acting beta₂-agonists (all agents - oral, inhaler, nebulizer, injection), short-acting anticholinergics (all agents - inhaler and nebulizer), combination short-acting beta-agonist plus anticholinergic in one inhaler (all agents - inhaler and nebulizer), methylxanthines, systemic corticosteroids (oral), and phosphodiesterase-4 inhibitors (oral)

Comparator Groups:

Eligible comparators are all inhaled long-acting agents (LABA, ICS, inhaled LAMA) in any combination and placebo. Concomitant COPD medications will be included if both groups receive the same interventions.

Outcome(s) of Interest:

Efficacy outcomes:

1. Proportion of patients with exacerbations (primary outcome of interest)
2. Number of hospitalizations (overall and due to exacerbations)
3. Number of emergency room visits (overall and due to exacerbations)
4. Function (e.g., 6 minute walk test, paced shuttle walk test)
5. Forced expiratory volume (FEV)
6. Quality of life
7. Number of patients with ischemic heart disease
8. Dyspnea
9. Mortality

Safety outcomes:

10. All harms
11. Serious harms
12. Withdrawals due to lack of efficacy
13. Treatment-related withdrawals
14. Fractures
15. Bone mineral density
16. Heart failure
17. Arrhythmia
18. Cardiovascular-related mortality
19. Pneumonia
20. Cataracts
21. Oral thrush
22. Palpitations
23. Headache
24. Constipation

25. Dry mouth

Notes: this list may be truncated if we identify many studies for inclusion, as this is a rapid review. We will not perform a meta-analysis (or network meta-analysis) on all of these outcomes and will work with all stakeholders to select the two most important efficacy outcomes and safety outcomes with sufficient data to conduct network meta-analysis. Prior to conducting network meta-analysis, we will ensure that all factors are considered (definition of outcomes, use of rescue medication, patient population, disease severity) because this analysis only is valid when homogenous studies and patient populations are included.

Included study designs:

Randomized controlled trials

Time: Studies of any duration will be included.

Other: We will limit inclusion to English for the ODPRN report. We will note the RCTs written in languages other than English and consider including these prior to publishing our systematic review in full. Studies will be excluded if they are animal studies or if there is no quantitative data to abstract (e.g. letters, commentaries).

Methods

The figure in Appendix 1 displays the general approach that we use at the Li Ka Shing Knowledge Institute of St. Michael's Hospital to conduct a systematic review.

Protocol development

The Preferred Reporting Items for Systematic reviews and Meta-analysis for Protocols (PRISMA-P) Statement will guide review reporting of our protocol [20]. A draft protocol will be circulated to receive feedback from key stakeholders including the OPDRN, clinicians pharmacoepidemiologists, and systematic review methodologists. The final protocol will be registered with the prospective systematic review registry PROSPERO [21].

Eligibility criteria

We use the Patients, Interventions, Comparators, Outcomes, Study designs and Time period (PICOST) framework (see above). The draft eligibility criteria can be found in Appendix 2.

Information sources and literature search

Comprehensive literature searches will be conducted by an experienced librarian (Becky Skidmore) in consultation with the team. We will search the MEDLINE, EMBASE, and Cochrane Library electronic databases from inception to January 2014. The preliminary MEDLINE search is presented in Appendix 3. The main (MEDLINE) search will be peer reviewed by another experienced librarian (Heather McDonald) using the Peer Review of Electronic Search Strategies (PRESS) checklist [22]. After this exercise, the MEDLINE search will be modified as necessary and the other databases will be searched in a similar manner. In order to identify unpublished and difficult to locate material (also called grey literature), we will search conference abstracts (many of these are identified through the electronic

searches), trial protocols (also often identified through the electronic searches), and trial registries (World Health Organization International Clinical Trials Registry Platform, which allows searching multiple trial registries simultaneously [23]). We will check the websites of manufacturers of the inhaled long-acting agents. We will contact authors of conference abstracts, trial protocols, and trial registries to determine whether the RCT has been published in full. If the RCT has not been published, we will request further information on the RCT methods to determine eligibility, as required. Unpublished data from conference abstracts fulfilling our eligibility criteria will be included only if the full publication or conference presentation is unobtainable. Literature saturation will be ensured by searching the reference lists of included studies and reference lists of relevant reviews [6-10, 15-19].

The results from the literature search will be uploaded to Synthesi.SR, online software created by our team [24]. Our software will be used for screening the citations resulting from the electronic database, as well as all potentially relevant full-text articles.

Study selection process

To ensure reliability, a training exercise will be conducted prior to commencing screening. Using the inclusion and exclusion criteria, a random sample of 25 titles and abstracts (also called citations) from the literature search will be screened by all team members. Inter-rater agreement for study inclusion will be calculated using percent agreement and if it is >90% across the team, we will proceed to the next stage. If poor agreement is found, the inclusion and exclusion criteria will be revised. Screening will only commence when the percent agreement is >90%. Two reviewers will screen citations for inclusion, independently (Level 1 screening). They will then independently review the full-text of potentially relevant articles to determine inclusion using the same inclusion and exclusion criteria (Level 2 screening). Conflicts will be resolved by discussion or the involvement of a third reviewer.

Data items and data abstraction process

We will abstract data on study characteristics (e.g., year of conduct [if not reported, we will use the year of publication], sample size, setting [e.g., hospital, community, multi-center, single center], country of study conduct [if not reported, we will use the country of origin of the first author], duration of treatment, timing of treatment [e.g., during the day or at night], duration of follow-up, intervention and comparator dosage, monotherapy, combination therapy), participant characteristics (e.g., number of patients, age mean and standard deviation, severity of COPD, how COPD was diagnosed), and the definitions of outcomes (e.g., exacerbations [e.g., number of patients with at least 1 exacerbation], hospitalizations [overall or due to exacerbations], function [e.g., 6-minute walk test, paced shuttle test], quality of life [e.g., St George respiratory questionnaire, considerations of night-time relief], serious adverse events [e.g., a harm resulting in hospitalization], arrhythmia [e.g., tachycardia, bradycardia]). This is particularly important for exacerbations, as the way that the trialists define this can result in biased estimates of treatment effect [25]. Finally, we will abstract the outcome results (e.g. number of patients with exacerbations, number of patients hospitalized) for the longest duration of follow-up only, as this is the most conservative approach. The data will be extracted and stored in Excel. The draft data abstraction form can be found in Appendix 4. We will create a “cheat sheet” that will accompany reviewers while they are performing data abstraction. This will allow them to navigate the Excel file and result in greater inter-rater reliability. Furthermore, we

will conduct a calibration exercise of the data abstraction form and cheat sheet amongst the team. This will entail the entire team conducting data abstraction on a random sample of 10 articles. Data abstraction will only commence when high agreement is achieved (e.g., only minor disagreements/recording errors noted across the team). The data abstraction form and cheat sheet will be revised, if low agreement is observed.

Since this systematic review is being completed in a short time-frame, only the outcome data will be abstracted in duplicate. Discrepancies will be resolved by discussion or the involvement of a third reviewer. Details relating to the study characteristics and patient characteristics will only be abstracted by one person for the ODPRN report. This will subsequently be conducted in duplicate prior to publication.

We suspect that multiple study publications may report data from the same study group (i.e., companion reports). When this occurs, the report with the most complete follow-up data will be included and used to abstract data. The other report(s) will provide supplementary data only. We also anticipate that studies may report a variety of time-points and where appropriate we will use subgroup analysis to explore this; if 2 studies from the same cohort of patients are reported, the outcome at the oldest age point will be included. We will contact the study authors for further information when the data are not clearly reported. Finally, we will search for errata and retractions for all of the included studies to ensure that the outcome data used in the analysis are correct.

Risk of bias appraisal process

We will appraise the included RCTs using the Cochrane Risk of Bias Tool [26]. This will be conducted by one reviewer for the ODPRN report. This will subsequently be conducted in duplicate prior to publication. We will also assess the studies using a modified McHarm tool [27] for the publication and not for the ODPRN report, due to time constraints. Publication bias will be assessed using funnel plots [28].

Synthesis of included studies

We will first describe our systematic review results, reporting study characteristics, patient characteristics, risk of bias results, and frequencies of outcomes across the included studies. Prior to considering meta-analysis, we will assess for statistical, clinical, and methodological heterogeneity. If extensive statistical (e.g., a statistically significant Q statistic [$p < 0.1$] for heterogeneity or an I^2 statistic greater than 75% [29]), clinical, or methodological heterogeneity [29] is observed we will conduct meta-regression analysis, if feasible depending on the number of eligible studies. The total number of covariates will be constrained so that it is equal to 1/10 the number of studies [30], due to issues with multiple testing in systematic reviews [29]. Meta-regression analysis will explore the influence of a few important factors, such as effect sizes and duration of follow-up. Both meta-analysis and meta-regression will be analyzed in the R software [31]. The relative risk will be calculated for dichotomous values and the mean difference will be calculated for continuous variables [32]. The standardized mean difference will be used to pool studies that use different scales for the same outcomes (e.g., quality of life). We anticipate that some of the included studies will not report all relevant data (e.g., standard deviations or standard errors). To include these studies in our analysis, the missing data will be imputed using the median standard deviations reported across the

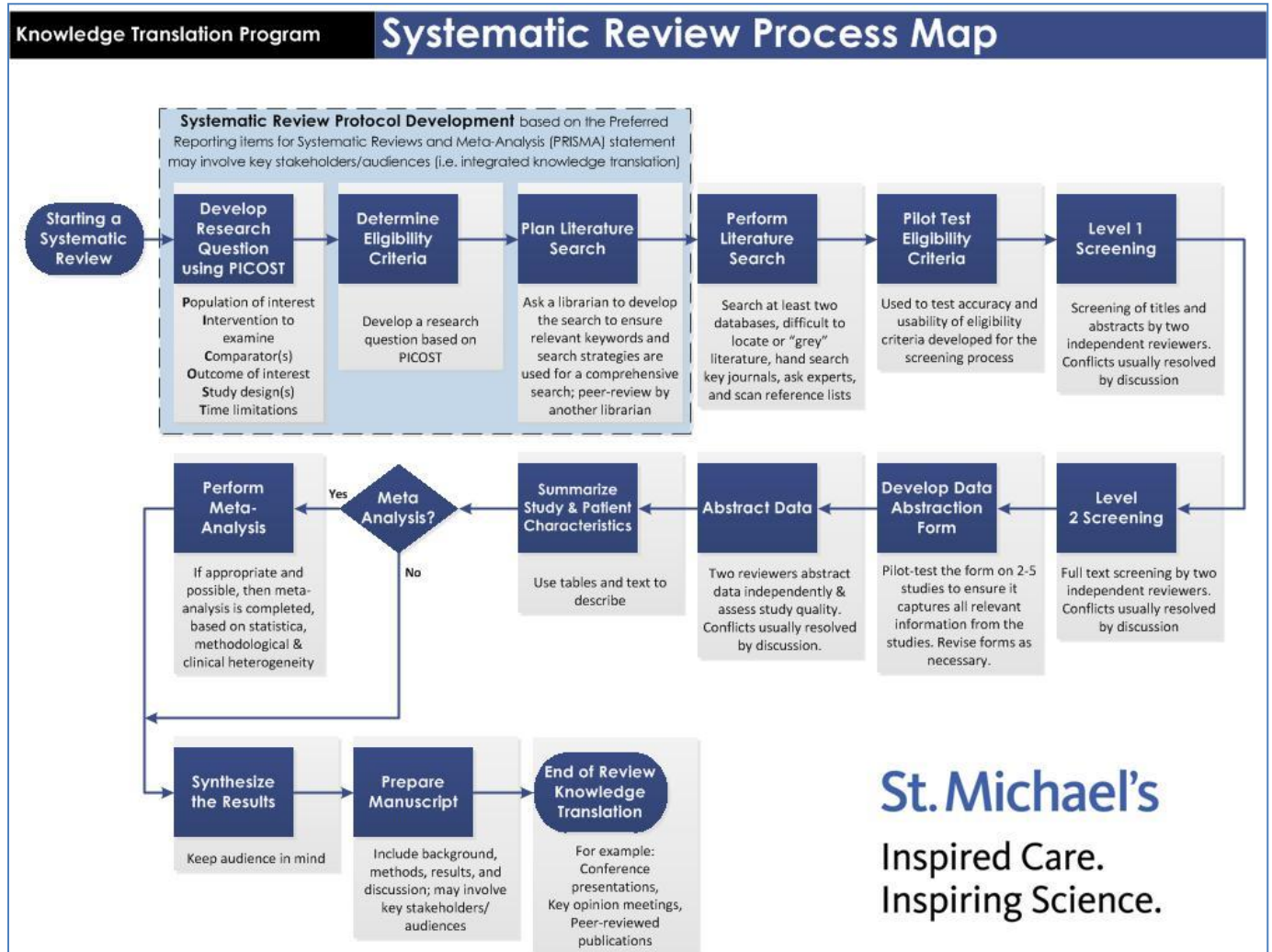
included RCTs or using those from similar RCTs [33].

We will explore the effects of subgroups on outcomes to establish the robustness of findings. We will limit the number of subgroup analysis, due to issues with multiple testing in systematic reviews [29]. Subgroups that we will explore include the diagnosis of COPD (e.g., according to the GOLD criteria [1] versus all others), severity of COPD (e.g., moderate-severe versus all others), gender, and definitions of outcomes (exacerbations in particular [25]).

Network meta-analysis will be conducted to derive the combined outcome effect size between each 2 comparisons, as well as rank the safety among all available interventions [34]. The placebo group will be used as a reference in the network meta-analysis. To facilitate the practicality of treatment comparisons, median rankings will be used as point estimates of intervention safety. We will use the NODE XL program to present the network meta-analysis results [35]. Network meta-analysis will be conducted in WinBUGS [36], a Bayesian software program used to build complex statistical models using Markov Chain Monte Carlo simulation.

This will be conducted using a burn-in sample of 50000, followed by 100000 samples for inference. Convergence of the Markov chain Monte Carlo simulation will be assessed with the Gelman-Rubin-Brooks plot and diagnostic test [37]. Default prior distributions (in all cases non-informative) will be adopted for all parameters in the model. Statistical significance will be expressed by 95% credible intervals that will be established using the 2.5 and 97.5 percentiles obtained via Markov Chain Monte Carlo simulation. We will interpret the 95% credible interval in a similar manner as confidence intervals are interpreted when they are derived using standard meta-analysis. The consistency of the results between direct versus indirect evidence will be compared using the node-splitting method [38].

APPENDIX 1: Systematic review process map



APPENDIX 2: Draft eligibility criteria

Level 1 screening:

1. Does this study include adult patients diagnosed with COPD?
YES _____
NO _____
UNCLEAR _____

2. Is this a randomized clinical trial?
YES _____
NO _____
UNCLEAR _____

3. Does this study examine ANY of the following agents: inhaled LABA (e.g., formoterol, indacaterol, salmeterol), ICS (e.g., beclomethasone, budesonide, fluticasone), combination LABA and ICS in one inhaler (e.g., formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone, vilanterol/fluticasone), and inhaled LAMA (adidinium bromide, glycoyrronium bromide, tiotropium) [in any combination]?
YES _____
NO _____
UNCLEAR _____

4. Does this study compare a relevant intervention to ANY of the following agents: inhaled LABA (e.g., formoterol, indacaterol, salmeterol), ICS (e.g., beclomethasone, budesonide, fluticasone), combination LABA and ICS in one inhaler (e.g., formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone, vilanterol/fluticasone), inhaled LAMA (adidinium bromide, glycoyrronium bromide, tiotropium), and placebo [in any combination]?
YES _____
NO _____
UNCLEAR _____

5. This study likely fulfills our eligibility criteria but is:
Not written in English _____ (note: will not fully exclude from the review)
A conference abstract (need to contact authors) _____
A trial protocol (need to contact authors) _____
A relevant systematic review (need to scan references) _____

Level 2 screening:

1. Does this study include adult patients diagnosed with COPD?
YES _____
NO _____
UNCLEAR _____
2. Is this a randomized clinical trial?
YES _____
NO _____
UNCLEAR _____
3. Does this study examine ANY of the following agents: inhaled LABA (e.g., formoterol, indacaterol, salmeterol), ICS (e.g., beclomethasone, budesonide, fluticasone), combination LABA and ICS in one inhaler (e.g., formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone, vilanterol/fluticasone), and inhaled LAMA (adidinium bromide, glycoyrronium bromide, tiotropium) [in any combination]?
YES _____
NO _____
UNCLEAR _____
4. Does this study compare a relevant intervention to ANY of the following agents: inhaled LABA (e.g., formoerol, arformoterol, indacaterol, salmeterol, tulobuterol), ICS (e.g., beclomethasone, budesonide, fluticasone), combination LABA and ICS in one inhaler (e.g., formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone, vilanterol/fluticasone), inhaled LAMA (adidinium bromide, glycoyrronium bromide, tiotropium), and placebo [in any combination]?
YES _____
NO _____
UNCLEAR _____
5. Does this study report on ANY of the following outcomes: proportion of patients with exacerbations, number of hospitalizations (overall and due to exacerbations), number of emergency room visits (overall and due to exacerbations), function, forced expiratory volume, quality of life, number of patients with pneumonia, number of patients with ischemic heart disease, mortality, harms (including all harms, serious harms, withdrawals due to lack of efficacy, treatment-related withdrawals, and the following specific harms: fractures, bone mineral density, heart failure, arrhythmia, cataracts, oral thrush, palpitations, headache, constipation, and dry mouth).
YES _____
NO _____
UNCLEAR _____
6. This study likely fulfills our eligibility criteria but:
Is not written in English _____ (note: will not fully exclude from the review)
Is a conference abstract (need to contact authors) _____
Is a trial protocol (need to contact authors) _____

Is a relevant systematic review (need to scan references) _____

Does not contain abstractable data (need to contact authors) _____

- ➔ If you answer NO to any of these questions, the citation/study will be excluded. All other citations/studies will be included. We will keep track of reviews that have potentially relevant material and will scan their reference lists to ensure all studies have been captured.

APPENDIX 3: Draft MEDLINE search

Database: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

Search Strategy:

-
- 1 exp Pulmonary Disease, Chronic Obstructive/
 - 2 exp Emphysema/ or exp Pulmonary Emphysema/
 - 3 ((chronic adj2 obstructi*) and (pulmonary or airway* or air way* or lung\$1 or airflow* or air flow*)).tw.
 - 4 (COPD or COAD).tw.
 - 5 (chronic adj2 bronchitis).tw.
 - 6 emphysema*.tw.
 - 7 or/1-6
 - 8 Formoterol*.tw,rn.
 - 9 (BD 40A or HSDB 7287 or Oxis or UNII-5ZZ84GCW8B).tw.
 - 10 (eformoterol or Foradil).tw.
 - 11 73573-87-2.rn.
 - 12 Indacaterol.tw,rn.
 - 13 (Arcapta or Onbrez or QAB 149 or QAB149 or UNII-8OR09251MQ).tw.
 - 14 312753-06-3.rn.
 - 15 Salmeterol*.tw,rn.
 - 16 (Aeromax or Astmerole or "GR 33343 X" or "GR 33343X" or HSDB 7315 or SN408D or UNII-214BC502BT).tw.
 - 17 89365-50-4.rn.
 - 18 Salmeterolxinafoate.tw,rn.
 - 19 (Ariol or Asmerole or Beglan or Betamican or Dilamax or Inaspir or Salmetedur or Serevent or Ultrabeta or UNII-6EW8Q962A5).tw.
 - 20 94749-08-3.rn.
 - 21 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta-agonist* or betaagonist* or beta-adrenergic* or adrenergic beta-receptor* or beta-receptor agonist* or beta-adrenoceptor agonist*)).tw.
 - 22 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta-2-agonist* or beta-2agonist* or beta-2-adrenergic* or adrenergic beta-2-receptor* or beta-2-receptor agonist* or beta-2-adrenoceptor agonist*)).tw.
 - 23 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta2-agonist* or beta2agonist* or beta2-adrenergic* or adrenergic beta2-receptor* or beta2-receptor agonist* or beta2- adrenoceptor agonist*)).tw.
 - 24 ((longacting or long-acting) and ("beta(2)-agonist*" or "beta(2)agonist*" or "beta(2)-adrenergic*" or "adrenergic beta(2)-receptor*" or "beta(2)-receptor agonist*" or "beta(2)-adrenoceptor agonist*")).tw.
 - 25 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (B2-agonist* or B2-adrenergic* or adrenergic B2-receptor* or B2-receptor agonist* or B2-adrenoceptor agonist*)).tw.
 - 26 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting)

and (B-2-agonist* or B-2-adrenergic* or adrenergic B-2-receptor* or B-2-receptor agonist* or B-2-adrenoceptor agonist*).tw.

27 (LABA or LABAs or Ultra-LABA* or UltraLABA*).tw.

28 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and bronchodilator*).tw.

29 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (betamimetic* or beta-mimetic*)).tw.

30 exp Adrenergic beta-Agonists/ or Bronchodilator Agents/

31 (longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting).tw.

32 30 and 31

33 or/21-29,32

34 Administration, Inhalation/

35 exp Aerosols/

36 (inhal* or aerosol*).tw.

37 or/34-36)

38 33 and 37

39 or/8-20,38

40 Beclomethasone/

41 (Aerobec or AeroBec Forte or Aldecin or Apo-Beclomethasone or Ascocortonyl or AsmabecClickhaler).tw.

42 (Beclamet or Beclazone or BecloAsma or Beclo AZU or Beclocort or Becloforte or Beclomet or Beclometason* or Beclomethasone or Beclorhinol or Becloturmant or Beclovent or Becodisk* or Beconase or Becotide or BemedrexEasyhaler or Bronchocort).tw.

43 (Ecobec or Filair or Junik or Nasobec Aqueous or Prolair or Propaderm or Qvar or Respocort or Sanasthmax or Sanasthmyl or Vancenase or Vanceril or Ventolair or Viarin).tw.

44 (BMJ 5800 or EINECS 224-585-9 or UNII-KGZ1SLC28Z).tw.

45 4419-39-0.rn.

46 Budesonide/

47 (Budesonide or Micronyl or Preferid or Pulmicort or Respules or Rhinocort or "S 1320" or Spirocort or Uceris or UNII-Q3OKS62Q6X).tw.

48 51333-22-3.rn.

49 Fluticasone.tw,rn.

50 (Cutivate or Flixonase or Flixotide or Flonase or Flovent or Fluticason* or HSDB 7740 or UNII-CUT2W21N7U).tw.

51 Glucocorticoids/

52 glucocorticoid*.tw.

53 Adrenal Cortex Hormones/

54 (corticoid* or corticosteroid* or cortico-steroid*).tw.

55 ((adrenal cortex or adrenal cortical) adj3 hormon*).tw.

56 ((adrenal cortex or adrenal cortical) adj3 steroid*).tw.

57 or/51-56

58 57 and 37

59 or/40-50,58

60 (Fluticasone adj3 salmeterol).tw,rn.

61 (Adoair or Advair or Foxair or "Quikhale SF" or Seretide or Viani).tw.
62 (formoterol adj3 mometasone).tw,rn.
63 (Zenhale or Dulera).tw.
64 (formoterol adj3 budesonide).tw,rn.
65 (Rilast or Symbicord or Symbicort or Vannair).tw.
66 (vilanterol adj3 fluticasone).tw,rn.
67 Breo Ellipta.tw.
68 or/60-67
69 tiotropium.tw,rn.
70 (BA 679 BR or BA 679BR or Spiriva or tiotropium or UNII-0EB439235F or UNII-XX112XZP0J).tw.
71 aclidiniumbromide.tw,rn.
72 (LAS 34273 or LAS W-330 or BretarisGenuair or EkliraGenuair or TudorzaPressair or UNII-UQW7UF9N91).tw.
73 glycopyrroniumbromide.tw,rn.
74 (erythro-glycopyrronium bromide or UNII-9SFK0PX55W).tw.
75 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (anticholinergic* or anti-cholinergic* or cholinolytic* or cholinergic-blocking or antimuscarinic* or anti-muscarinic* or ((cholinergic or acetylcholine or muscarinic) adj3 antagonist*))).tw.
76 (LAMA or LAMAs or Ultra-LAMA* or UltraLAMA*).tw.
77 Muscarinic Antagonists/ or Cholinergic Antagonists/
78 77 and 31
79 75 or 76 or 78
80 79 and 37
81 or/69-74,80
82 39 or 59 or 68 or 81
83 7 and 82
84 randomized controlled trial.pt.
85 controlled clinical trial.pt.
86 randomized.ab.
87 placebo.ab.
88 clinical trials as topic/
89 randomly.ab.
90 trial.ti.
91 or/84-90
92 83 and 91
93 exp Animals/ not (exp Animals/ and Humans/)
94 92 not 93

APPENDIX 4: Draft data abstraction form

Study Characteristics

1. First author and year of publication
2. Reference ID number
3. Year of study conduct
4. Sample size
5. Setting (e.g., hospital, community, multi-center, single center)
6. Country of study conduct (if not reported, use the country of origin of the first author)
7. Duration of treatment
8. Total duration of follow-up (includes duration of treatment and subsequent follow-up)
9. Intervention(s) in each arm
10. Comparator (e.g., placebo)

Patient Characteristics

11. Number of patients
12. Mean age and standard deviation (if not reported, the range or interquartile range will be used)
13. Age category (adult, elderly [aged 65 years and greater], adult plus elderly)
14. Percent gender
15. Diagnosis of COPD (e.g., using the GOLD criteria [1])
16. Severity of COPD (e.g., mild-moderate, moderate-severe, very severe)

Outcome definitions

17. Definition of exacerbations (e.g., at least 1 exacerbation per patient)
18. Definition of hospitalizations (e.g., overall, due to exacerbations)
19. Definition of function (e.g., 6-minute walk test, unpaced shuttle test)
20. Definition of quality of life (e.g., St George respiratory questionnaire)
21. Definition of serious adverse events (e.g., harm resulting in hospitalization)
22. Definition of arrhythmia (e.g., tachycardia, bradycardia)

Outcome results

23. Exacerbations (number of patients in each group)
24. Emergency room visits (number of patients in each group)
25. Function
26. Forced expiratory volume
27. Quality of life
28. Pneumonia (number of patients in each group)
29. Ischemic heart disease (number of patients in each group)
30. Mortality (number of patients in each group)
31. All harms (number of patients in each group)
32. Withdrawals due to lack of efficacy (number of patients in each group)

33. Treatment-related withdrawals (number of patients in each group)
34. Serious harms (number of patients in each group)
35. Fractures (number of patients in each group)
36. Bone mineral density
37. Heart failure (number of patients in each group)
38. Arrhythmia (number of patients in each group)
39. Cataracts (number of patients in each group)
40. Oral thrush (number of patients in each group)
41. Palpitations (number of patients in each group)
42. Headache (number of patients in each group)
43. Constipation (number of patients in each group)
44. Dry mouth (number of patients in each group)

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