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Effect of beta-blockers on clinical, safety and health related quality of life outcomes in patients with chronic obstructive pulmonary disease (COPD): A protocol for a systematic literature review and meta-analysis with multiple treatment comparison

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Abstract

Introduction

Patients with chronic obstructive pulmonary disease (COPD) who have a clinical indication for beta-blocker therapy, are often not prescribed such medication, despite evidence suggesting that beta-blockers are not associated with adverse respiratory outcomes. The primary objective of this systematic review and meta-analysis is to examine the class effect of beta-blocker use in patients with COPD, with a focus on patient-centric endpoints including, clinical, safety and health related quality of life (HRQoL) outcomes. A secondary objective is to explore potential within-class variation in the effects of beta-blockers among patients with COPD, and rank them according to their benefit.

Methods and analysis

MEDLINE, Embase and The Cochrane Library will be systematically searched to identify randomised controlled trials (RCTs) and other prospective and interventional studies of beta-blocker use in patients with COPD, reporting on the outcomes of interest. Relative treatment effects in terms of mortality, COPD exacerbations, all-cause hospitalisations, lung function, and HRQoL will be summarised by meta-analysis. Individual treatments (agents) will be compared in a Baysesian network meta-analysis (NMA) including RCT and observational data, if feasible.

Ethics and dissemination

The results of the study will be submitted for publication in a peer-reviewed journal.

Prospero registration number: CRD42018098983.

Strengths and limitations of this study

- To our knowledge, this is the first review including a quantitative summary of HRQoL outcomes for patients with COPD who are receiving beta-blocker therapy.
- The systematic review will include evidence from both RCT and real world data, which will extend the generalisability of the findings to patients outside of a tightly controlled RCT environment.
- It may not be possible to conduct a multiple treatment comparison for the less reported outcomes in our selected patient population (i.e. HRQoL, exacerbations).

- Subgroup analyses may not be possible due to a lack of data. This may limit the applicability of the results and recommendations for specific patient subpopulations (e.g. patients with COPD and concomitant coronary artery disease).

Background

Chronic obstructive pulmonary disease (COPD) is a leading cause of death in both the United States (US) and Europe and often co-exists with cardiovascular disease (CVD). Beta-blockers are recommended in several CVDs due to their associated reductions in mortality and morbidity, as shown in clinical trials of patients with heart failure (HF)[1], post myocardial infarction (MI)[2] and acute coronary syndromes (ACS)[3].

Whilst COPD guidelines[4] recommend the use of cardio-selective beta-blockers, where beta-blocker therapy is indicated, patients with concomitant COPD and CVD are often not prescribed these medications due to fear of respiratory deterioration[5]. This under-utilisation of beta-blockers in patients with COPD patients has been demonstrated in recent studies of HF, including a nationwide study from Denmark where only 60% of patients with comorbid HF and COPD reportedly received a beta-blocker[6], whilst the proportion was as low as 18% in Scotland[7]. Other studies suggest a significant association of COPD with (under)use of beta-blocker therapy at discharge after ACS, with as many as one third of patients not receiving the medication[8].

Contrary to the clinical concern regarding the risks of beta-blocker therapy in COPD, evidence is emerging that beta-blockers may even confer potential benefits for reasons beyond CVD-related outcomes in patients with COPD. Two Cochrane reviews showed that cardio-selective beta-blockers administered to patients with COPD or mild to moderate reversible airway disease did not exhibit detrimental effects on lung function[9,10]. Both those with mild or moderate reversible airway disease as well as COPD patients had no significant change in their FEV1 levels after taking beta-blockers when compared to placebo, irrespective of the duration

and timing of treatment and beta-blockers were well tolerated in patients with comorbid HF, hypertension or angina[9].

Observational studies[11, 12], post-hoc analyses from RCTs[13] and meta-analyses[14] have demonstrated the mortality benefits of beta-blockers extend to patients with COPD and CVD, as well as in subgroups of patients hospitalised for COPD exacerbations (AECOPD). Indeed, the fact that the primary cause of hospitalisation in COPD is CVD rather than respiratory failure, emphasises the importance of cardiovascular risk management in such patients[15]. Other outcomes have been less studied; for instance little attention has been given to the effect of beta-blockers on other COPD-related outcomes such as acute exacerbations or functional status, which may be more reflective of the overall burden of chronic disease and are relevant predictors of hospitalisation. In addition, previous systematic reviews and meta-analyses have focused on short term findings, particularly when using RCT data, which is frequently characterised by short follow up times, ranging from single dose studies up to 16 weeks follow-up[9].

In the present study, we seek to investigate the effects of beta-blocker use on short and long term outcomes in patients with COPD, by conducting a systematic literature review (SLR) and quantitative synthesis of clinical and observational data. We will include a range of patient-centric outcomes, including clinical, safety and HRQoL effects and we will use a meta-analytical approach to demonstrate the class effect of beta-blockers and, if feasible, perform a network meta-analysis (NMA) to elucidate within-class differences in beta-blocker effects. Demonstration of consistent benefits associated with beta-blocker use in patients with COPD and comorbid CVD, across a range of endpoints, would strengthen the argument in favour of their use in this population.

Rationale for conducting the review

Whilst there is evidence on the lack of a detrimental effect of beta-blockers in patients with COPD with regards to lung function, previous reviews have only studied cardio-selective beta-

blockers. In addition there has been no systematic assessment of the literature on the long term effects on COPD exacerbation rate, mortality, hospitalisations, or HRQoL outcomes associated with beta-blocker use in this population. The review by Salpeter et al. (2002) did not include observational data and focused only on FEV1 with the latest data published prior to 2010, Etminan et al. (2012) investigated mortality alone, but no within-class comparison of individual beta-blockers was conducted. We will perform an updated review including studies of cardio selective and non-cardio selective beta-blockers, and contemporary data.

Furthermore, this is the first systematic review to incorporate clinical trial and observational data which will enable investigation of short and long term outcomes in COPD. If feasible, we will also conduct a network meta-analysis comparing the effects of different beta-blockers including a ranking according to their benefits in patients with COPD.

Objectives

We will assess the clinical efficacy (e.g. FEV1, rates of exacerbations, and mortality), safety (e.g. discontinuations) and HRQoL (e.g. exercise capacity) of beta-blockers in patients with COPD from RCTs and observational studies.

We will also determine the effect(s) of individual beta-blockers on patient prognosis as compared to placebo. If the data permit, we will compare beta-blockers against one another in an NMA for each outcome of interest and explore subgroup effects for specific combinations of COPD and CVD (e.g. patients with COPD and concomitant HF, post MI or ACS). Observational data will be integrated in the NMA where feasible.

Rationale for including observational data

We do not expect to find large RCTs of beta-blockers for some of the outcomes[16], such as . COPD exacerbations or hospitalisations. In order to increase the power and precision of

treatment effect estimates we will include observational studies (prospective and longitudinal). In addition, this will allow generalisation of our findings to real world populations and enable the investigation of longer term outcomes, specifically adverse events, which may not be captured in RCTs with short follow up times.

We will weigh observational data in order to minimise the potential introduction of bias relating to their use.

Aims

1. To identify and critically assess the evidence for beta-blocker use in patients with COPD, with respect to clinical and HRQoL outcomes (SLR and meta-analysis).
2. To compare and contrast within-class effects of beta-blockers in patients with COPD, on clinical and HRQoL outcomes (NMA).

Research questions

1. What are the beneficial or adverse effects of beta-blocker use in patients with COPD with regards to clinical, safety and HRQoL outcomes? (SLR and meta-analysis)
2. Is there a difference in outcomes between different beta-blockers for patients with COPD? If so, which agents offer the best prognosis for such patients? (NMA)

Methods

This study will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines[17]. This protocol is registered in PROSPERO (CRD42018098983). Search algorithms will be generated using the PICOs criteria reflecting the research questions.

Population

Patients with COPD will be defined as those demonstrated by a baseline FEV1 of <80% normal predicted value, consistent with the definition used by the guidelines of the American Thoracic Society[18] or with a clinical (physician) diagnosis of COPD. Patients will be

included if they are aged 35 years old or over. We will exclude patients diagnosed with asthma.

Interventions and comparators

We will include studies where any of the following beta-blockers were investigated, whether compared against placebo or another beta-blocker, and given either as a single dose or for an extended period of time:

- Acebutolol, atenolol, betaxolol , bisoprolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, celiprolol, esmolol, levobunolol, oxprenolol

Studies investigating palliative care alone or a "watch and wait" intervention will be excluded.

Outcomes

Clinical and safety:

- COPD exacerbations (rate, time to exacerbation)
- All-cause mortality
- Hospitalisation rate (all cause, and due to COPD exacerbations)
- Lung function (FEV1)
- Adverse events (any, including non-specific adverse events, and, discontinuation of beta- blocker therapy due to adverse events)

HRQoL (measured as change from baseline):

- Six minute walk test (6MWT)
- incremental shuttle walk test (ISWT)
- Short form 36 (SF-36), EQ-5D – generic
- St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)
- Chronic Respiratory Questionnaire (CRQ).
- COPD Assessment Test (CAT)

Publications investigating in vitro, animal, foetal, molecular, genetic, pathologic, or pharmacokinetic/pharmacodynamic outcomes without outcomes of interest reported will be excluded.

Study design

We will include RCT and observational studies (prospective cohort studies), reporting on outcomes of patients with COPD. Studies including a mixed population (e.g. COPD and asthma) will be excluded unless they present outcomes separately for the population of interest. Narrative publications, non-systematic reviews, case studies, case reports, and editorials will also be excluded.

Search methods and data sources

Clinical efficacy, safety and HRQoL searches will be conducted in MEDLINE and Embase via Ovid, and The Cochrane Collection Central Register of Clinical Trials (CENTRAL) with no temporal limits. We will also search ClinicalTrials.gov (www.clinicaltrials.gov). The search strategy is available in the Supplementary Material.

Manual searching

Reference lists of accepted publications as well as relevant systematic reviews will be manually searched for additional references.

Selection of Eligible Studies

Title and abstract screening

Each abstract will be reviewed by two independent investigators to assess eligibility for inclusion in the study according to the pre-defined inclusion and exclusion criteria. Any disagreements will be resolved through discussion. Where resolution cannot be reached, a third (senior) investigator will make the final decision. For all abstracts deemed eligible for inclusion during the first level of review, full-text articles will be retrieved and reviewed.

Full- text screening

Full papers will be reviewed by a single investigator. All publications rejected at this stage will be confirmed by a second investigator. For each excluded study, a specific reason for exclusion will be provided and validated by the second investigator. A third investigator will be consulted to resolve any disagreements as necessary.

Data Extraction

For each included study, data will be extracted on study design, patient characteristics, interventions and outcomes using a Microsoft Excel template developed by the first author with input from the second and third authors. Data will be extracted independently by a single investigator and then validated by a second investigator. Differences in extraction will be resolved through discussion or by a third investigator.

Risk of bias assessment

The quality of the RCTs will be assessed with the Cochrane tool for assessing risk of bias in RCTs[19]. Observational studies will be assessed using ROBINS-1[19]. Two investigators will independently complete the appropriate 'Risk of bias' form for each included study. Conflicts will be resolved as described above. Each study will be defined as being at high, low or unclear risk of bias.

Data synthesis

In order to investigate the clinical, safety and HRQoL effects of beta-blocker use in patients with COPD, we will conduct the following analyses:

1. Meta-analysis of beta-blocker class effect

We will conduct a meta-analysis for each of the outcomes included in the review. For risks, we will extract or manually calculate the incidence and/or prevalence for the population included in each trial and will meta-analyse relative risks (RR) with 95% confidence intervals (95%CI). For continuous variables, we will extract mean differences and 95% CI. If clinical homogeneity and the risk of bias are both low, we will pool the results using either fixed-

effect or random-effects modelling, depending on the degree of statistical heterogeneity (we will consider $I^2 > 50\%$ as a cut-off point for the use of a random effects model). If the risk of bias is high or study heterogeneity is high, we will not pool individual studies, but present a narrative synthesis.

2. NMA of individual beta-blockers

In the absence of evidence presenting a direct head-to-head comparison of treatments (e.g comparing A to B), an unbiased estimate from an RCT comparing treatments A and C and from and RCT comparing B and C can be derived in an indirect treatment comparison (NMA) (Figure 1). An NMA allows evidence from direct and indirect comparisons to be summarised in a weighted average for all possible comparisons. This analysis will assume that the relative differences between the treatments are exchangeable and apply to all of the included studies.

Figure 1. NMA incorporating direct and indirect evidence

For each outcome of interest, in first instance we will include RCT data alone and in a second stage we will add data from propensity matched or adjusted studies (i.e. observational studies) using Bayesian hierarchical modelling. This allows for weighting by study design and provides effect estimates within each study type, as well as overall. Whilst observational data is prone to more bias than RCT data, we believe its inclusion will offset the limitation of RCT data for the analysis of rarely reported outcomes such as quality of life and will help increase generalisability.

We expect little or no RCT data for some outcomes e.g. exacerbation and hospitalisation rates. If this is found to be the case, and where the data permit, we will pool results from included

studies, irrespective of study design and perform a meta-analysis of the relative risk of exacerbation or hospitalisation (due to any reason) secondary to beta-blocker use.

Network maps will be presented to illustrate the treatments that are directly compared against each other and the amount of evidence available for each of the treatments. Separate network maps will be presented for each outcome and per study design.

We will report relative risks (and 95% CrI [Credible Intervals]) to compare rates and mean differences for continuous variables. If pooling is possible we will use OpenBugs version 3.2.3 and R version 3.4.4 software.

Presentation of results

1) Meta-analysis

Forest plots will be presented for each outcome of interest. A funnel plot will be constructed to identify evidence of publication bias.

2) NMA

Results for each endpoint will be presented in league tables for all possible comparisons between treatments of interest along with a pairwise probability (i.e., the probability of the treatment being better than a specified comparator).

Forest plots showing the relative treatment effects for each treatment in the network versus the reference treatment (i.e. placebo) will be presented.

SUCRA (surface under the cumulative ranking) diagrams showing the probability that a given treatment ranks first, second, third, and so on, among all treatments evaluated in the NMA (with regards to the particular endpoint being considered) will also be presented and should be interpreted alongside the forest plots[20]. These diagrams will also give the SUCRA percentages of total possible area-under-the-curve when ranking treatments, such that the closer a percentage is to 100%, the higher the treatment ranking is relative to all other treatments.

Subgroup analysis

Subgroup analyses will be conducted to assess the impact of clinically meaningful treatment modifiers (e.g. number and type of comorbidities). The following analyses will be considered, where the data permit: patients with COPD and HF, post MI, atrial fibrillation, hypertension (or other CVD).

Contributions: Claudia Gulea (CG) is the guarantor. CG drafted the protocol and developed the search strategy. Jennifer K Quint (JKQ) and Rosita Zakeri (RZ) advised on inclusion and exclusion criteria and critically reviewed the protocol. All authors read, provided feedback and approved the final manuscript.

Competing interests: None declared.

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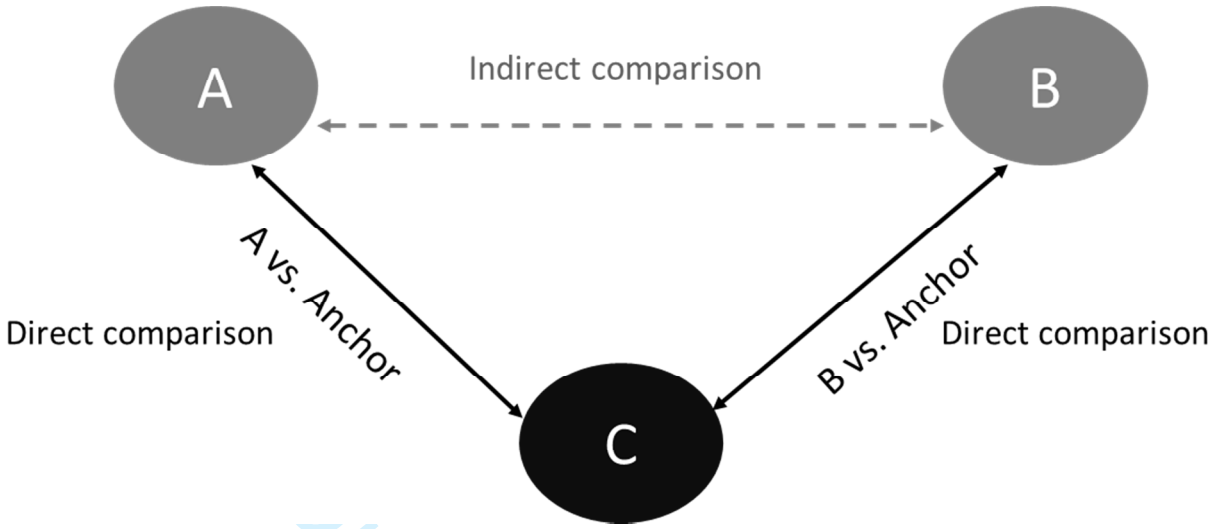

Search strategy

Embase and Medline (via Ovid)

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$)).mp.
6.	COAD.mp
7.	COBD.mp
8.	AECB.mp
9.	COPD.mp
10.	Or/1-9
11.	(beta blocker$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or sotalol or celiprolol or esmolol or levobunolol or oxprenolol).mp.
12.	adrenergic beta-antagonists.mp. or exp Adrenergic beta-Antagonists/
13.	((adrenergic* and antagonist*) or (adrenergic* and block*) or (adrenergic* and beta-receptor*) or (beta-adrenergic* and block*) or beta-blocker*andadrenergic*).mp.
14.	or/11-13
15.	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
16.	10 and 14 and 15
17.	exp cohort studies/
18.	exp longitudinal study/
19.	exp prospective study/
20.	cohort$.tw.
21.	controlled clinical trial.pt.
22.	Or/17-21
23.	(conference review or conference abstract or comment or editorial or meta-analysis or practice-guideline or guideline$ or review or letter or journal or correspondence or short-survey or note).pt.
24.	RCTs: 10 and 14 and 15 not 23 – limit to humans
25.	Observational studies and non-randomized trials: 10 and 14 and 22 not 23 – limit to humans

Central database

1.	(Pulmonary Disease, Chronic Obstructive).ti.ab.
2.	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
3.	emphysema$.mp.
4.	(chronic$ adj3 bronchiti$) .mp.

5.	(obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)) .mp.
6.	COPD.mp.
7.	COAD.mp.
8.	COBD.mp.
9.	AECB.mp.
10.	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
11.	(beta blocker$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or sotalol or celiprolol or esmolol or levobunolol or oxprenolol):ti,ab (adrenergic* and antagonist*) or (adrenergic* and block*) or (adrenergic* and beta-receptor*) or (beta-adrenergic* and block*) or (beta-blocker* and adrenergic*)
12.	(adrenergic* and antagonist*) or (adrenergic* and block*) or (adrenergic* and beta-receptor*) or (beta-adrenergic* and block*) or (beta-blocker* and adrenergic*)
13.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
14.	#10 or #11 or #12
15.	#13 and #14 – limit to Humans

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review - page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such – Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number - page 2
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author – page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review – page 12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments – This is not an amendment for a previous protocol
Support:		
Sources	5a	Indicate sources of financial or other support for the review – page 12
Sponsor	5b	Provide name for the review funder and/or sponsor - page 12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol - page 12
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known – page 4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) – page 6-7
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review - page 8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage – page 8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated – Supplementary material
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review – page 9

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) page 8-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators page 9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications page 6-7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale page 5, page 7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis page 9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised page 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) page 9-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) – page 12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned page 10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Page 11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) page 9-11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Effect of beta-blockers on clinical, safety, health related quality of life and functional outcomes in patients with chronic obstructive pulmonary disease (COPD): A protocol for a systematic literature review and meta-analysis with multiple treatment comparison

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Abstract

Introduction

Patients with chronic obstructive pulmonary disease (COPD) who have a clinical indication for beta-blocker therapy, are often not prescribed such medication, despite evidence suggesting that beta-blockers are not associated with adverse respiratory outcomes. The primary objective of this systematic review and meta-analysis is to examine the class effect of beta-blocker use in patients with COPD. We will focus on a broad range of endpoints including, clinical, safety, and patient-centric outcomes such as health related quality of life (HRQoL) and functional capacity. A secondary objective is to explore potential within-class variation in the effects of beta-blockers among patients with COPD, and rank individual agents according to their relative benefit(s).

Methods and analysis

MEDLINE, Embase The Cochrane Library and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases will be systematically searched, from inception to present, to identify randomised controlled trials (RCTs) and other prospective and interventional studies of beta-blocker use in patients with COPD, which report on the outcomes of interest. Relative treatment effects with respect to mortality, COPD exacerbations, all-cause hospitalisation, lung function, HRQoL and exercise capacity will be summarised by meta-analysis. Individual treatments (agents) will be compared in a Bayesian network meta-analysis (NMA) including RCT and observational data, if feasible.

Ethics and dissemination

The results of the study will be submitted for publication in a peer-reviewed journal. Only previously published aggregate data will be used for the purpose of this review.

Prospero registration number: CRD42018098983.

Strengths and limitations of this study

- To our knowledge, this is the first review including a quantitative summary of HRQoL outcomes for patients with COPD who are receiving beta-blocker therapy.

- The systematic review will include evidence from both RCT and real world (observational) data, which will extend the generalisability of the findings to patients outside of a tightly controlled RCT environment.
- It may not be possible to conduct a multiple treatment comparison for the less reported outcomes in our selected patient population (i.e. HRQoL, exacerbations).
- Subgroup analyses may not be possible due to a lack of data. This may limit the recommendations for specific patient subpopulations (e.g. patients with COPD and concomitant coronary artery disease).

Background

Chronic obstructive pulmonary disease (COPD) is a leading cause of death in both the United States (US) and Europe and often co-exists with cardiovascular disease (CVD)[1]. Beta-blockers are recommended in several CVD states due to their beneficial effects on mortality and morbidity, as shown in clinical trials of patients with heart failure (HF)[2], post myocardial infarction (MI)[3] and acute coronary syndromes (ACS)[4].

Whilst COPD guidelines[5] recommend the use of cardio-selective beta-blockers, , patients with concomitant COPD and CVD are often not prescribed these medications due to fear of respiratory deterioration[6]. Concerns include a reduction in patients' forced expiratory volume in one second (FEV1) as well as diminished response to the standard COPD therapy (i.e. beta-agonists) in the long term[7]. Although several studies have shown reduced lung function, tolerability rates amongst COPD patients have been good (i.e. >80%[8]). It is therefore unclear whether the drop in FEV1 would have a significant impact on long-term outcomes including mortality.

This under-utilisation of beta- blockers in patients with COPD has been demonstrated in recent studies of HF, including a nationwide study from Denmark where only 60% of patients with comorbid HF and COPD reportedly received a beta-blocker[9], and a further study in Scotland where the proportion was as low as 18%[10]. Other studies suggest a significant association of

COPD with underuse of beta-blocker therapy at discharge after ACS, with as many as one third of patients not receiving the medication[11].

Contrary to clinical concerns regarding the risks of beta-blocker therapy in COPD, evidence is accumulating that beta-blockers may confer potential benefits for reasons beyond CVD-related outcomes in patients with COPD. Two Cochrane reviews showed that cardio-selective beta-blockers administered to patients with COPD or mild to moderate reversible airway disease did not exhibit detrimental effects on lung function[12,13]. Patients with mild or moderate reversible airway disease as well as COPD had no significant change in their FEV1 after taking beta-blockers when compared to placebo. This effect was significant irrespective of the duration and timing of treatment and beta-blockers were well tolerated in patients with comorbid HF, hypertension or angina[12].

Observational studies[14, 15], post-hoc analyses from RCTs[16] and meta-analyses[17] have demonstrated that mortality benefits of beta-blockers extend to patients with COPD and CVD, as well as in subgroups of patients hospitalised for acute exacerbations of COPD (AECOPD). The fact that the primary cause of hospitalisation in COPD is CVD rather than respiratory failure, emphasises the importance of cardiovascular risk management in such patients[18]. However, other COPD-related outcomes have been less well studied; for instance little attention has been given to the effect of beta-blockers on rates of acute exacerbation or functional status, which may be more reflective of the overall burden of chronic disease and are relevant predictors of hospitalisation. Previous systematic reviews and meta-analyses have focused on short term findings, particularly when considering RCT data only, which is frequently characterised by short follow up times, ranging from single dose studies up to 16 weeks follow-up[12].

In the present study, we seek to investigate the effects of beta-blocker use on short term (at the end of an RCT or less than 6 weeks - whichever is earliest) and long term (any time after the end of the intervention) outcomes in patients with COPD, by conducting a systematic literature review (SLR) and quantitative synthesis of clinical trials and observational data. We will include

a broad range of outcomes, including clinical, safety and HRQoL effects and we will use a meta-analytical approach to demonstrate the class effect of beta-blockers and, if feasible, perform a network meta-analysis (NMA) to elucidate within-class differences in beta-blocker effects. Demonstration of consistent benefits associated with beta-blocker use in patients with COPD and comorbid CVD, across a range of endpoints, would strengthen the argument in favour of their use in this population.

Rationale for conducting the review

Whilst there is evidence on the lack of a detrimental effect of beta-blockers in patients with COPD with regards to lung function, previous reviews have only studied cardio-selective beta-blockers. In addition there has been no systematic assessment of the literature on the long term effects on COPD exacerbation rate, mortality, hospitalisations, HRQoL or functional outcomes associated with beta-blocker use in this population. The review by Salpeter et al. (2002) did not include observational data and focused only on FEV1 with the latest data published prior to 2010, and Etminan et al. (2012) investigated mortality alone, but did not quantitively compare individual beta-blockers. We will perform an updated review including studies of cardio selective and non-cardio selective beta-blockers.

Furthermore, this is the first systematic review to incorporate clinical trial and observational data which will enable investigation of short and long term outcomes in COPD. If feasible, we will also conduct a network meta-analysis comparing the effects of different beta-blockers including a ranking according to their benefits in patients with COPD.

Objectives

We will assess the clinical efficacy (e.g. FEV1, rates of exacerbations, and mortality), safety (e.g. discontinuations), HRQoL (e.g.symptom burden) and functional status (e.g. exercise capacity) of beta-blockers in patients with COPD from RCTs and observational studies.

We will also determine the effect(s) of individual beta-blockers on patient prognosis as compared to placebo. If the data permit, we will compare beta-blockers against one another in an NMA for each outcome of interest and explore subgroup effects for specific combinations of COPD and CVD (e.g. patients with COPD and concomitant HF, post MI or ACS). Observational data will be integrated in the NMA where feasible.

Rationale for including observational data

We do not expect to find large RCTs of beta-blockers for some outcomes[19], such as COPD exacerbations or hospitalisations. Therefore, in order to increase the power and precision of treatment effect estimates, we will include observational studies (prospective and longitudinal). This will allow generalisation of our findings to real world populations and enable the investigation of longer term outcomes, specifically adverse events, which may not be captured in RCTs with short follow up times.

We will review the degree of bias of observational data and take this into account in our analysis.

Aims

1. To identify and critically assess the evidence for beta-blocker use in patients with COPD, with respect to clinical, safety, HRQoL and functional outcomes (SLR and meta-analysis).
2. To compare and contrast within-class effects of beta-blockers in patients with COPD, on clinical, safety, HRQoL and functional outcomes (NMA).

Research questions

1. What are the beneficial or adverse effects of beta-blocker use in patients with COPD with regards to clinical, safety, HRQoL and functional outcomes? (SLR and meta-analysis)
2. Is there a difference in outcomes between different beta-blockers for patients with COPD? If so, which agents offer the best prognosis for such patients? (NMA)

Methods

This study will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines[20]. This protocol is registered in PROSPERO (CRD42018098983). Search algorithms will be generated using the PICOs criteria reflecting the research questions.

Population

Patients with COPD will be defined as those demonstrated by a baseline FEV1 of <80% normal predicted value, a FEV1/FVC[1] ratio < 70% consistent with the definition used by the guidelines of the American Thoracic Society[21] or with a clinical (physician) diagnosis of COPD. Patients will be included if they are aged 35 years old or over. We will exclude patients diagnosed with asthma.

Interventions and comparators

We will include studies where any of the following beta-blockers were investigated, whether compared against placebo or another beta-blocker, and given either as a single dose or for an extended period of time:

- Acebutolol, atenolol, betaxolol , bisoprolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, celiprolol, esmolol, levobunolol, oxprenolol

Studies investigating palliative care alone or a "watch and wait" intervention will be excluded.

Outcomes

Clinical and safety:

- COPD exacerbations (rate, time to exacerbation)
- All-cause mortality
- Hospitalisation rate (all cause, and due to COPD exacerbations)

[1] FVC = forced vital capacity

- Lung function (FEV1)
- Adverse events (any, including non-specific adverse events, and, discontinuation of beta- blocker therapy due to adverse events)

HRQoL (measured as change from baseline):

- Short form 36 (SF-36), EQ-5D – generic
- St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)
- Chronic Respiratory Questionnaire (CRQ)
- COPD Assessment Test (CAT)

Functional outcomes (measured as change from baseline):

- Six minute walk test (6MWT)
- Incremental shuttle walk test (ISWT)

Publications investigating in vitro, animal, foetal, molecular, genetic, pathologic, or pharmacokinetic/pharmacodynamic outcomes without outcomes of interest reported will be excluded.

Study design

We will include RCT and observational studies (prospective cohort studies), reporting on outcomes of patients with COPD. Studies including a mixed population (e.g. COPD and asthma) will be excluded unless they present outcomes separately for the population of interest. Narrative publications, non-systematic reviews, case studies, case reports, and editorials will also be excluded.

Search methods and data sources

Clinical efficacy, safety and HRQoL searches will be conducted in MEDLINE, Embase and CINAHL via Ovid, and The Cochrane Collection Central Register of Clinical Trials (CENTRAL) with no temporal limits. We will also search ClinicalTrials.gov (www.clinicaltrials.gov). Articles written

in languages other than English will be excluded. The search strategy is available in the Supplementary Material.

Manual searching

Reference lists of accepted publications as well as relevant systematic reviews will be manually searched for additional references.

Selection of Eligible Studies

Title and abstract screening

Each title and abstract will be reviewed by two independent investigators to assess eligibility for inclusion in the study according to the pre-defined inclusion and exclusion criteria. Any disagreements will be resolved through discussion. Where resolution cannot be reached, a third (senior) investigator will make the final decision. For all abstracts deemed eligible for inclusion during the first level of review, full-text articles will be retrieved and reviewed.

Full- text screening

Full papers will be reviewed by a two independent investigators. All publications rejected at this stage will be confirmed by a second investigator. For each excluded study, a specific reason for exclusion will be provided and validated by the third investigator. A third investigator will be consulted to resolve any disagreements as necessary.

Patient and Public Involvement

As this is a retrospective review of data that has already been collected, patients were not involved in development of the research question or the design of this study at this stage.

Data Extraction

For each included study, data will be extracted on study design, patient characteristics, interventions and outcomes using a Microsoft Excel template developed by the first author with input from the second and third authors. Data elements to be extracted include :

- Study characteristics (country, study design, follow-up time, aims, statistical analysis)
- Population: Demographic information (sex, age, ethnicity), sampling methods, inclusion/exclusion criteria, disease severity, comorbidities

- Interventions and comparators: type of beta-blocker, median, total treatment duration
- Outcomes : definition of outcome, time point of assessment, value at baseline/time point, change in value from baseline/time point

Data will be extracted independently by two investigators. Differences in extraction will be resolved through discussion or by a third investigator.

Risk of bias assessment

The quality of the RCTs will be assessed with the Cochrane tool for assessing risk of bias in RCTs[22]. Observational studies will be assessed using ROBINS-1[22]. Two investigators will independently complete the appropriate 'Risk of bias' form for each included study. Conflicts will be resolved as described above. Each study will be defined as being at high, low or unclear risk of bias.

Data synthesis

In order to investigate the clinical, safety HRQoL and functional effects of beta-blocker use in patients with COPD, we will conduct the following analyses:

1. Meta-analysis of beta-blocker class effect

We will conduct a meta-analysis for each of the outcomes included in the review. For risks, we will extract or manually calculate the incidence and/or prevalence for the population included in each trial and will meta-analyse relative risks (RR) with 95% confidence intervals (95% CI). For continuous variables, we will extract mean differences and 95% CI. If clinical homogeneity and the risk of bias are both low, we will pool the results using either fixed-effect or random-effects modelling, depending on the degree of statistical heterogeneity. Higgins et al. (2002) [23]suggest heterogeneity is moderate at I^2 of 50%, therefore we will consider $I^2 > 50\%$ as a cut-off point for the use of a random effects model. If the risk of bias is high or study heterogeneity is high, we will not pool individual studies, but present a narrative synthesis.

2. NMA of individual beta-blockers

In the absence of evidence presenting a direct head-to-head comparison of treatments (e.g. comparing A to B), an unbiased estimate from an RCT comparing treatments A and C and from and RCT comparing B and C can be derived in an indirect treatment comparison (NMA) (Figure 1). An NMA allows evidence from direct and indirect comparisons to be summarised in a weighted average for all possible comparisons. This analysis will assume that the relative differences between the treatments are exchangeable and apply to all of the included studies.

Figure 1. NMA incorporating direct and indirect evidence

A feasibility assessment analysing sources of heterogeneity will be conducted on all included studies in the systematic review. This will evaluate whether NMAs can be carried out for the outcomes of interest, by taking into consideration the similarity of patient characteristics, number of studies identified, follow up times, shape of network and other factors.

For each outcome for which an NMA will be feasible, we will initially include RCT data alone and in a second stage we will add data from propensity matched or adjusted studies (i.e. observational studies) using Bayesian hierarchical modelling. This is a statistical model which estimates the parameters of the posterior distribution using the Bayesian method. This allows for weighting by study design and provides effect estimates within each study type as well as overall. For example, evidence from RCTs will be first combined to produce estimates; the same will be done for observational studies and in a third step, both estimates can be combined to obtain overall results.

Whilst observational data is prone to more bias than RCT data, we believe its inclusion will offset the limitation of RCT data for the analysis of rarely reported outcomes such as quality of life and will help increase generalisability.

We expect little or no RCT data for some outcomes e.g. exacerbation and hospitalisation rates. If this is found to be the case, and where the data permit, we will pool results from included studies, irrespective of study design and perform a meta-analysis of the relative risk of exacerbation or hospitalisation (due to any reason) secondary to beta-blocker use.

Network maps will be presented to illustrate the treatments that are directly compared against each other and the amount of evidence available for each of the treatments. Separate network maps will be presented for each outcome and per study design.

We will report relative risks (and 95% CrI [Credible Intervals]) to compare rates and mean differences for continuous variables. If pooling is possible we will use OpenBugs version 3.2.3 and R version 3.4.4 software.

Presentation of results

As data permits, results will be presented for both short and long-term outcomes.

1) Meta-analysis

Forest plots will be presented for each outcome of interest. A funnel plot will be constructed to identify evidence of publication bias.

2) NMA

Results for each endpoint will be presented in league tables for all possible comparisons between treatments of interest along with a pairwise probability (i.e., the probability of the treatment being better than a specified comparator).

Forest plots showing the relative treatment effects for each treatment in the network versus the reference treatment (i.e. placebo) will be presented.

SUCRA (surface under the cumulative ranking) diagrams showing the probability that a given treatment ranks first, second, third, and so on, among all treatments evaluated in the NMA (with regards to the particular endpoint being considered) will also be presented and should be interpreted alongside the forest plots[24]. These diagrams will also give the SUCRA percentages of

total possible area-under-the-curve when ranking treatments, such that the closer a percentage is to 100%, the higher the treatment ranking is relative to all other treatments.

Subgroup analysis

Subgroup analyses will be conducted to assess the impact of clinically meaningful treatment modifiers (e.g. number and type of comorbidities). The following analyses will be considered, where the data permit: patients with COPD and HF, post MI, atrial fibrillation, hypertension (or other CVD).

Discussion

One important limitation of this review confounding by contraindication. This refers to the situation where a drug is knowingly withheld by a treating clinician due to fears the medication would cause negative effects. In this case, differences in outcomes between treated and untreated patients are associated with a contraindication for therapy in the untreated patients. This lends itself well to the clinical scenario of beta-blocker administration to patients with COPD since clinicians are hesitant to prescribe the medication. This type of confounding could lead to an underestimation of the relative risk between those who receive treatment versus those who do not.

The main strength of this review is the inclusion of a broad range of outcomes, including quality of life, of relevance to patients with COPD in relation to beta-blocker use. A quantitative investigation of the trade-off between patient-centric outcomes and clinical and safety effects in this context could contribute new arguments to support the utilisation of beta-blockers in COPD.

Contributions: Claudia Gulea (CG) is the guarantor. CG drafted the protocol and developed the search strategy. Jennifer K Quint (JKQ) and Rosita Zakeri (RZ) advised on inclusion and exclusion criteria and critically reviewed the protocol. All authors read, provided feedback and approved the final manuscript.

Competing interests: None declared.

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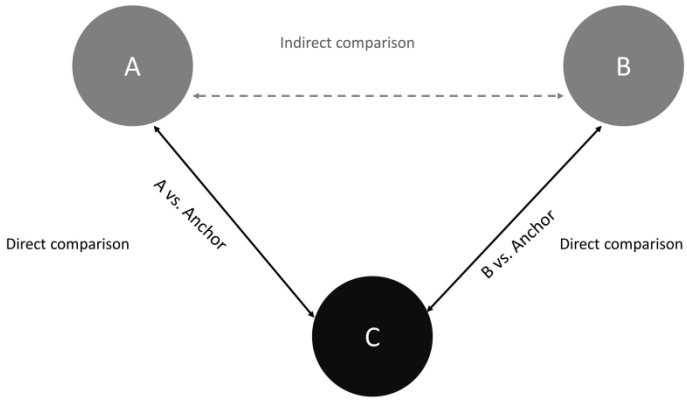

Figure 1. NMA incorporating direct and indirect evidence

338x190mm (300 x 300 DPI)

Search strategy

Embase and Medline (via Ovid)

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$)).mp.
6.	COAD.mp
7.	COBD.mp
8.	AECB.mp
9.	COPD.mp
10.	Or/1-9
11.	(beta blocker$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or sotalol or celiprolol or esmolol or levobunolol or oxprenolol).mp.
12.	adrenergic beta-antagonists.mp. or exp Adrenergic beta-Antagonists/
13.	((adrenergic* and antagonist*) or (adrenergic* and block*) or (adrenergic* and beta-receptor*) or (beta-adrenergic* and block*) or beta-blocker*andadrenergic*).mp.
14.	or/11-13
15.	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
16.	10 and 14 and 15
17.	exp cohort studies/
18.	exp longitudinal study/
19.	exp prospective study/
20.	cohort$.tw.
21.	controlled clinical trial.pt.
22.	Or/17-21
23.	(conference review or conference abstract or comment or editorial or meta-analysis or practice-guideline or guideline$ or review or letter or journal or correspondence or short-survey or note).pt.
24.	RCTs: 10 and 14 and 15 not 23 – limit to humans
25.	Observational studies and non-randomized trials: 10 and 14 and 22 not 23 – limit to humans

Central database

1.	(Pulmonary Disease, Chronic Obstructive).ti.ab.
2.	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
3.	emphysema$.mp.
4.	(chronic$ adj3 bronchiti$) .mp.

5.	(obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)) .mp.
6.	COPD.mp.
7.	COAD.mp.
8.	COBD.mp.
9.	AECB.mp.
10.	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
11.	(beta blocker$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or sotalol or celiprolol or esmolol or levobunolol or oxprenolol):ti,ab (adrenergic* and antagonist*) or (adrenergic* and block*) or (adrenergic* and beta-receptor*) or (beta-adrenergic* and block*) or (beta-blocker* and adrenergic*)
12.	(adrenergic* and antagonist*) or (adrenergic* and block*) or (adrenergic* and beta-receptor*) or (beta-adrenergic* and block*) or (beta-blocker* and adrenergic*)
13.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
14.	#10 or #11 or #12
15.	#13 and #14 – limit to Humans

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review - page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such – Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number - page 2
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author – page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review – page 12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments – This is not an amendment for a previous protocol
Support:		
Sources	5a	Indicate sources of financial or other support for the review – page 12
Sponsor	5b	Provide name for the review funder and/or sponsor - page 12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol - page 12
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known – page 4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) – page 6-7
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review - page 8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage – page 8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated – Supplementary material
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review – page 9

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) page 8-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators page 9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications page 6-7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale page 5, page 7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis page 9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised page 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) page 9-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) – page 12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned page 10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Page 11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) page 9-11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Effect of beta-blocker therapy on clinical outcomes, safety, health-related quality of life and functional capacity in patients with chronic obstructive pulmonary disease (COPD): A protocol for a systematic literature review and meta-analysis with multiple treatment comparison

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Effect of beta-blocker therapy on clinical outcomes, safety, health-related quality of life and functional capacity in patients with chronic obstructive pulmonary disease (COPD): A protocol for a systematic literature review and meta-analysis with multiple treatment comparison

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Abstract

Introduction

Patients with chronic obstructive pulmonary disease (COPD) who have a clinical indication for beta-blocker therapy, are often not prescribed such medication, despite evidence suggesting that beta-blockers are not associated with adverse respiratory outcomes. The primary objective of this systematic review and meta-analysis is to examine the class effect of beta-blocker use in patients with COPD. We will focus on a broad range of endpoints including, clinical, safety, and patient-centric outcomes such as health related quality of life (HRQoL) and functional capacity. A secondary objective is to explore potential within-class variation in the effects of beta-blockers among patients with COPD, and rank individual agents according to their relative benefit(s).

Methods and analysis

MEDLINE, Embase The Cochrane Library and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases will be systematically searched, from inception to present, to identify randomised controlled trials (RCTs) and other prospective and interventional studies of beta-blocker use in patients with COPD, which report on the outcomes of interest. Relative treatment effects with respect to mortality, COPD exacerbations, all-cause hospitalisation, lung function, HRQoL and exercise capacity will be summarised by meta-analysis. Individual treatments (agents) will be compared in a Bayesian network meta-analysis (NMA) including RCT and observational data, if feasible.

Ethics and dissemination

The results of the study will be submitted for publication in a peer-reviewed journal. Only previously published aggregate data will be used for the purpose of this review.

Prospero registration number: CRD42018098983.

Strengths and limitations of this study

- To our knowledge, this is the first review including a quantitative summary of HRQoL outcomes for patients with COPD who are receiving beta-blocker therapy.

- The systematic review will include evidence from both RCT and real world (observational) data, in order to extend the generalisability of the findings to patients encountered in clinical practice outside of a tightly controlled RCT environment.
- It may not be possible to conduct a multiple treatment comparison for outcomes that are less frequently reported in our selected patient population (e.g. HRQoL, COPD exacerbation rate).
- Subgroup analyses may not be possible due to a lack of data. This may limit the recommendations for specific patient subpopulations (e.g. patients with concomitant COPD and coronary artery disease).

Background

Chronic obstructive pulmonary disease (COPD) is a leading cause of death in both the United States (US) and Europe and often co-exists with cardiovascular disease (CVD)[1]. Beta-blockers are recommended in several CVD states due to their beneficial effects on mortality and morbidity, as demonstrated in clinical trials including patients with heart failure (HF)[2], post myocardial infarction (MI)[3] and acute coronary syndromes (ACS)[4].

Whilst COPD guidelines[5] recommend the use of cardio-selective beta-blockers, patients with concomitant COPD and CVD are often not prescribed these medications due to fear of respiratory deterioration[6]. Concerns include a beta-blocker induced reduction in patients' forced expiratory volume in one second (FEV1) as well as diminished response to the standard COPD therapy (i.e. beta-agonists) in the long term[7]. Although several studies have suggested reduced lung function may be associated with beta-blocker use, tolerability rates amongst COPD patients have been good (i.e. >80%[8]). It is therefore unclear whether the observed drop in FEV1 would have a significant impact on long-term outcomes including mortality.
Under-utilisation of beta- blockers in patients with COPD has been demonstrated in recent studies of concomitant HF, including a nationwide study from Denmark where only 60% of patients with comorbid HF and COPD reportedly received a beta-blocker[9]. A further study in

Scotland reported a proportion as low as 18%[10]. Studies in other patient populations suggest a significant underuse of beta-blocker therapy associated with COPD at discharge after ACS, with as many as one third of patients not receiving the medication[11].

Contrary to the aforementioned concerns regarding potential risks of beta-blocker therapy in COPD, evidence is accumulating that beta-blockers may importantly confer potential benefits for non-CVD related outcomes in patients with COPD. Two Cochrane reviews reported that cardio-selective beta-blockers administered to patients with COPD or mild to moderate reversible airway disease did not exhibit detrimental effects on lung function[12,13]. Patients with mild or moderate reversible airway disease as well as COPD had no significant change in their FEV1 after taking beta-blockers when compared to placebo. This effect was significant irrespective of the duration and timing of treatment and beta-blockers were well tolerated in patients with comorbid HF, hypertension or angina[12].

Observational studies[14, 15], post-hoc analyses from RCTs[16] and meta-analyses[17] have demonstrated that mortality benefits of beta-blockers extend to patients with COPD and CVD, as well as in subgroups of patients hospitalised for acute exacerbations of COPD (AECOPD). Indeed the primary cause of hospitalisation in COPD is CVD rather than respiratory failure, emphasising the importance of cardiovascular risk management in such patients[18]. However, other COPD-related outcomes have been less well studied; for instance little attention has been given to the effect of beta-blockers on rates of acute exacerbation of COPD or patients' functional status, which may be more reflective measures of the overall burden of chronic disease and are relevant predictors of hospitalisation. Previous systematic reviews and meta-analyses have focused on short term findings, particularly when exclusively considering RCT data, which is frequently characterised by short follow up times, ranging from single dose studies up to 16 weeks' follow-up[12].

In the present study, we seek to investigate the effects of beta-blocker use on short term (at the end of an RCT or less than 6 weeks - whichever is earliest) and long term (any time after the

end of the intervention) outcomes in patients with COPD, by conducting a systematic literature review (SLR) and quantitative synthesis of contemporary clinical trials and observational data. We will include a broad range of outcomes, including clinical, safety and HRQoL effects and we will use a meta-analytical approach to demonstrate the class effect of beta-blockers. If feasible, we will perform a network meta-analysis (NMA) to elucidate within-class differences in beta-blocker effects. Demonstration of consistent benefits associated with beta-blocker use in patients with COPD and comorbid CVD, across a range of endpoints, would strengthen the argument in favour of their use in this population.

Rationale for conducting the review

Whilst there is evidence available to suggest a lack of detrimental effect of beta-blockers in patients with COPD with regards to lung function, previous reviews have only studied cardio-selective beta- blockers. In addition there has been no systematic assessment of the literature regarding the long term effects of beta-blocker therapy on COPD exacerbation rate, mortality, hospitalisations, HRQoL or functional outcomes in this population. A review by Salpeter et al. (2002) did not include observational data and focused only on FEV1, summarising data published prior to 2010, while Etminan et al. (2012) investigated mortality alone, but did not quantitatively compare individual beta-blockers. We will perform an updated review including studies of cardio selective and non-cardio selective beta-blockers, where the information is available.

Finally, this is also the first systematic review to incorporate both clinical trial and observational data to enable investigation of short and long term outcomes in COPD. If feasible, we will also conduct a network meta-analysis comparing the effects of different beta-blockers, including a ranking according to their benefits in patients with COPD.

Objectives

We will assess the clinical efficacy (e.g. FEV1, rates of exacerbations, and mortality), safety (e.g. discontinuations), HRQoL (e.g. symptom burden) and functional status (e.g. exercise capacity) of beta-blockers in patients with COPD from RCTs and observational studies.

We will also determine the effect(s) of individual beta-blockers on patient prognosis as compared to placebo. If the data permit, we will compare beta-blockers against one another in an NMA for each outcome of interest and explore subgroup effects for specific combinations of COPD and CVD (e.g. patients with COPD and concomitant HF, post MI or ACS). Observational data will be integrated in the NMA where feasible.

Rationale for including observational data

We do not expect to find large RCTs of beta-blockers for some outcomes[19], such as COPD exacerbations or hospitalisations. Therefore, in order to increase the power and precision of treatment effect estimates, we will include observational studies (prospective and longitudinal). This will allow generalisation of our findings to real world populations and enable the investigation of longer term outcomes, specifically adverse events, which may not be captured in RCTs with short follow up times.

We will review the degree of bias of observational data and take this into account in our analysis.

Aims

1. To identify and critically assess the evidence for beta-blocker use in patients with COPD, with respect to clinical, safety, HRQoL and functional outcomes (SLR and meta-analysis).
2. To compare and contrast within-class effects of beta-blockers in patients with COPD, on clinical, safety, HRQoL and functional outcomes (NMA).

Research questions

1. What are the beneficial or adverse effects of beta-blocker use in patients with COPD with regards to clinical, safety, HRQoL and functional outcomes? (SLR and meta-analysis)
2. Is there a difference in outcomes between different beta-blockers for patients with COPD? If so, which agents offer the best prognosis for such patients? (NMA)

Methods

This study will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines[20]. This protocol is registered in PROSPERO (CRD42018098983). Search algorithms will be generated using the PICOs criteria reflecting the research questions.

Population

Patients with COPD will be defined as those demonstrated by a baseline FEV1 of <80% normal predicted value, a FEV1/FVC[1] ratio < 70% consistent with the definition used by the guidelines of the American Thoracic Society[21] or with a clinical (physician) diagnosis of COPD. Patients will be included if they are aged 35 years old or over. We will exclude patients diagnosed with asthma.

Interventions and comparators

We will include studies where any of the following beta-blockers were investigated, whether compared against placebo or another beta-blocker, and given either as a single dose or for an extended period of time:

- Acebutolol, atenolol, betaxolol , bisoprolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, celiprolol, esmolol, levobunolol, oxprenolol

Studies investigating palliative care alone or a "watch and wait" intervention will be excluded.

[1] FVC = forced vital capacity

Outcomes

Clinical and safety:

- COPD exacerbations (rate, time to exacerbation)
- All-cause mortality
- Hospitalisation rate (all cause, and due to COPD exacerbations)
- Lung function (FEV1)
- Adverse events (any, including non-specific adverse events, and, discontinuation of beta- blocker therapy due to adverse events)

HRQoL (measured as change from baseline):

- Short form 36 (SF-36), EQ-5D – generic
- St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)
- Chronic Respiratory Questionnaire (CRQ)
- COPD Assessment Test (CAT)

Functional outcomes (measured as change from baseline):

- Six minute walk test (6MWT)
- Incremental shuttle walk test (ISWT)

Publications investigating in vitro, animal, foetal, molecular, genetic, pathologic, or pharmacokinetic/pharmacodynamic outcomes without outcomes of interest reported will be excluded.

Study design

We will include RCT and observational studies (prospective cohort studies), reporting on outcomes of patients with COPD. Studies including a mixed population (e.g. COPD and asthma) will be excluded unless they present outcomes separately for the population of interest. Narrative publications, non-systematic reviews, case studies, case reports, and editorials will also be excluded.

Search methods and data sources

Clinical efficacy, safety and HRQoL searches will be conducted in MEDLINE, Embase and CINAHL via Ovid, and The Cochrane Collection Central Register of Clinical Trials (CENTRAL) with no temporal limits. We will also search ClinicalTrials.gov (www.clinicaltrials.gov). Articles written in languages other than English will be excluded. The search strategy is available in the Supplementary Material.

Manual searching

Reference lists of accepted publications as well as relevant systematic reviews will be manually searched for additional references.

Selection of Eligible Studies

Title and abstract screening

Each title and abstract will be reviewed by two independent investigators to assess eligibility for inclusion in the study according to the pre-defined inclusion and exclusion criteria. Any disagreements will be resolved through discussion. Where resolution cannot be reached, a third (senior) investigator will make the final decision. For all abstracts deemed eligible for inclusion during the first level of review, full-text articles will be retrieved and reviewed.

Full- text screening

Full papers will be reviewed by two independent investigators. All publications rejected at this stage will be confirmed by a second investigator. For each excluded study, a specific reason for exclusion will be provided and validated by the third investigator. A third investigator will be consulted to resolve any disagreements as necessary.

Patient and Public Involvement

As this is a retrospective review of data that has already been collected, patients were not involved in development of the research question or the design of this study at this stage.

Data Extraction

For each included study, data will be extracted on study design, patient characteristics, interventions and outcomes using a Microsoft Excel template developed by the first author with input from the second and third authors. Data elements to be extracted include :

- Study characteristics (country, study design, follow-up time, aims, statistical analysis)
- Population: Demographic information (sex, age, ethnicity), sampling methods, inclusion/exclusion criteria, disease severity, comorbidities
- Interventions and comparators: type of beta-blocker, median, total treatment duration
- Outcomes : definition of outcome, time point of assessment, value at baseline/time point, change in value from baseline/time point

Data will be extracted independently by two investigators. Differences in extraction will be resolved through discussion or by a third investigator.

Risk of bias assessment

The quality of the RCTs will be assessed with the Cochrane tool for assessing risk of bias in RCTs[22]. Observational studies will be assessed using ROBINS-1[22]. Two investigators will independently complete the appropriate 'Risk of bias' form for each included study. Conflicts will be resolved as described above. Each study will be defined as being at high, low or unclear risk of bias. The quality of evidence contributing to the quantitative analysis will be assessed using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [23] criteria.

Data synthesis

In order to investigate the clinical, safety HRQoL and functional effects of beta-blocker use in patients with COPD, we will conduct the following analyses:

1. Meta-analysis of beta-blocker class effect

We will conduct a meta-analysis for each of the outcomes included in the review. For risks, we will extract or manually calculate the incidence and/or prevalence for the population included in each trial and will meta-analyse relative risks (RR) with 95% confidence intervals

(95% CI). For continuous variables, we will extract mean differences and 95% CI. If clinical homogeneity and the risk of bias are both low, we will pool the results using either fixed-effect or random-effects modelling, depending on the degree of statistical heterogeneity. Higgins et al. (2002) [24] suggest heterogeneity is moderate at I^2 of 50%, therefore we will consider $I^2 > 50\%$ as a cut-off point for the use of a random effects model. If the risk of bias is high or study heterogeneity is high, we will not pool individual studies, but present a narrative synthesis.

2. NMA of individual beta-blockers

In the absence of evidence presenting a direct head-to-head comparison of treatments (e.g. comparing A to B), an unbiased estimate from an RCT comparing treatments A and C and from and RCT comparing B and C can be derived in an indirect treatment comparison (NMA) (Figure 1). An NMA allows evidence from direct and indirect comparisons to be summarised in a weighted average for all possible comparisons. This analysis will assume that the relative differences between the treatments are exchangeable and apply to all of the included studies.

Figure 1. NMA incorporating direct and indirect evidence

A feasibility assessment analysing sources of heterogeneity will be conducted on all included studies in the systematic review. This will evaluate whether NMAs can be carried out for the outcomes of interest, by taking into consideration the similarity of patient characteristics, number of studies identified, follow up times, shape of network and other factors.

For each outcome for which an NMA will be feasible, we will initially include RCT data alone and in a second stage we will add data from propensity matched or adjusted studies (i.e. observational studies) using Bayesian hierarchical modelling. This is a statistical model which estimates the parameters of the posterior distribution using the Bayesian method. This allows for weighting by study design and provides effect estimates within each study type as well as

overall. For example, evidence from RCTs will be first combined to produce estimates; the same will be done for observational studies and in a third step, both estimates can be combined to obtain overall results.

Whilst observational data is prone to more bias than RCT data, we believe its inclusion will offset the limitation of RCT data for the analysis of rarely reported outcomes such as quality of life and will help increase generalisability.

We expect little or no RCT data will be available for some outcomes e.g. exacerbation and hospitalisation rates. If this is found to be the case, and where the data permit, we will pool results from included studies, irrespective of study design and perform a meta-analysis of the relative risk of exacerbation or hospitalisation (due to any reason) secondary to beta-blocker use.

Network maps will be presented to illustrate the treatments that are directly compared against each other and the amount of evidence available for each of the treatments. Separate network maps will be presented for each outcome and per study design.

We will report relative risks (and 95% CrI [Credible Intervals]) to compare rates and mean differences for continuous variables. If pooling is possible we will use OpenBugs version 3.2.3 and R version 3.4.4 software.

Presentation of results

As data permits, results will be presented for both short and long-term outcomes.

1) Meta-analysis

Forest plots will be presented for each outcome of interest. A funnel plot will be constructed to identify evidence of publication bias.

2) NMA

Results for each endpoint will be presented in league tables for all possible comparisons between treatments of interest along with a pairwise probability (i.e., the probability of the treatment being better than a specified comparator).

Forest plots showing the relative treatment effects for each treatment in the network versus the reference treatment (i.e. placebo) will be presented.

SUCRA (surface under the cumulative ranking) diagrams showing the probability that a given treatment ranks first, second, third, and so on, among all treatments evaluated in the NMA (with regards to the particular endpoint being considered) will also be presented and should be interpreted alongside the forest plots[25]. These diagrams will also give the SUCRA percentages of total possible area-under-the-curve when ranking treatments, such that the closer a percentage is to 100%, the higher the treatment ranking is relative to all other treatments.

Subgroup analysis

Subgroup analyses will be conducted to assess the impact of clinically meaningful treatment modifiers (e.g. number and type of comorbidities). The following analyses will be considered, where the data permit: patients with COPD and HF, post MI, atrial fibrillation, hypertension (or other CVD).

Discussion

One important limitation of this review is confounding by contraindication. This refers to the situation where a drug is knowingly withheld by a treating clinician due to fears the medication would cause negative effects. In this case, differences in outcomes between treated and untreated patients may be associated with a contraindication for therapy in the untreated patients. This lends itself well to the clinical scenario of beta-blocker administration to patients with COPD since clinicians are hesitant to prescribe the medication. This type of confounding could lead to an underestimation of the relative risk between those who receive treatment versus those who do not.

However, a key strength of this review is the inclusion of a broad range of outcomes, including quality of life, of relevance to patients with COPD in relation to beta-blocker use. A quantitative investigation of the trade-off between patient-centric outcomes and clinical and safety effects

in this context could contribute new arguments to support the utilisation of beta-blockers in COPD.

Contributions: Claudia Gulea (CG) is the guarantor. CG drafted the protocol and developed the search strategy. Jennifer K Quint (JKQ) and Rosita Zakeri (RZ) advised on inclusion and exclusion criteria and critically reviewed the protocol. All authors read, provided feedback and approved the final manuscript.

Competing interests: None declared.

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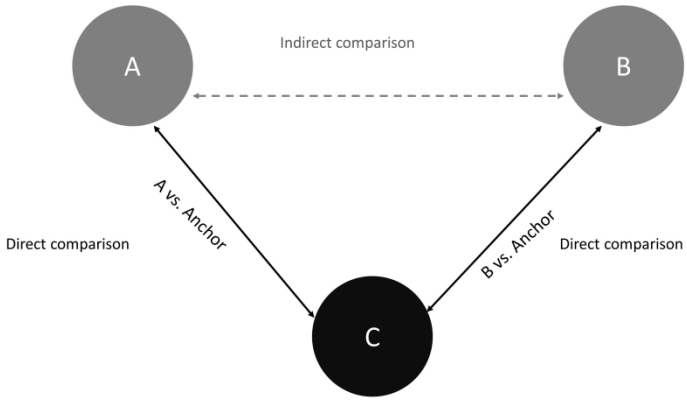

Figure 1. NMA incorporating direct and indirect evidence

338x190mm (300 x 300 DPI)

Search strategy

Embase and Medline (via Ovid)

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$)).mp.
6.	COAD.mp
7.	COBD.mp
8.	AECB.mp
9.	COPD.mp
10.	Or/1-9
11.	(beta blocker$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or sotalol or celiprolol or esmolol or levobunolol or oxprenolol).mp.
12.	adrenergic beta-antagonists.mp. or exp Adrenergic beta-Antagonists/
13.	((adrenergic* and antagonist*) or (adrenergic* and block*) or (adrenergic* and beta-receptor*) or (beta-adrenergic* and block*) or beta-blocker*andadrenergic*).mp.
14.	or/11-13
15.	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
16.	10 and 14 and 15
17.	exp cohort studies/
18.	exp longitudinal study/
19.	exp prospective study/
20.	cohort$.tw.
21.	controlled clinical trial.pt.
22.	Or/17-21
23.	(conference review or conference abstract or comment or editorial or meta-analysis or practice-guideline or guideline$ or review or letter or journal or correspondence or short-survey or note).pt.
24.	RCTs: 10 and 14 and 15 not 23 – limit to humans
25.	Observational studies and non-randomized trials: 10 and 14 and 22 not 23 – limit to humans

Central database

1.	(Pulmonary Disease, Chronic Obstructive).ti.ab.
2.	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
3.	emphysema$.mp.
4.	(chronic$ adj3 bronchiti$) .mp.

5.	(obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)) .mp.
6.	COPD.mp.
7.	COAD.mp.
8.	COBD.mp.
9.	AECB.mp.
10.	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
11.	(beta blocker$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or sotalol or celiprolol or esmolol or levobunolol or oxprenolol):ti,ab (adrenergic* and antagonist*) or (adrenergic* and block*) or (adrenergic* and beta-receptor*) or (beta-adrenergic* and block*) or (beta-blocker* and adrenergic*)
12.	(adrenergic* and antagonist*) or (adrenergic* and block*) or (adrenergic* and beta-receptor*) or (beta-adrenergic* and block*) or (beta-blocker* and adrenergic*)
13.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
14.	#10 or #11 or #12
15.	#13 and #14 – limit to Humans

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review - page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such – Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number - page 2
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author – page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review – page 12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments – This is not an amendment for a previous protocol
Support:		
Sources	5a	Indicate sources of financial or other support for the review – page 12
Sponsor	5b	Provide name for the review funder and/or sponsor - page 12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol - page 12
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known – page 4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) – page 6-7
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review - page 8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage – page 8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated – Supplementary material
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review – page 9

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) page 8-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators page 9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications page 6-7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale page 5, page 7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis page 9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised page 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) page 9-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) – page 12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned page 10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Page 11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) page 9-11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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