Cochrane Library

Cochrane Database of Systematic Reviews

Oral xanthine derivatives (theophylline and doxofylline) for patients with stable chronic obstructive pulmonary disease (COPD) (Protocol)

García Morales OM, Rojas-Reyes MX, Dennis RJ

García Morales OM, Rojas-Reyes MX, Dennis RJ.
Oral xanthine derivatives (theophylline and doxofylline) for patients with stable chronic obstructive pulmonary disease (COPD).
Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD012748.
DOI: 10.1002/14651858.CD012748.

www.cochranelibrary.com

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Protocol]

Oral xanthine derivatives (theophylline and doxofylline) for patients with stable chronic obstructive pulmonary disease (COPD)

Olga M García Morales[1,2], Maria Ximena Rojas-Reyes[3], Rodolfo J Dennis[3,4]

[1]Department of Internal Medicine, Faculty of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia. [2]Pulmonary Unit, Department of Internal Medicine, Hospital Universitario San Ignacio, Bogotá, Colombia. [3]Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia. [4]Research Department, Fundacion Cardioinfantil Instituto de Cardiologia, Bogotá, Colombia

Contact address: Olga M García Morales, Department of Internal Medicine, Faculty of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia. garcia.olga@javeriana.edu.co, milelinda@gmail.com.

Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 8, 2017.

Citation: García Morales OM, Rojas-Reyes MX, Dennis RJ. Oral xanthine derivatives (theophylline and doxofylline) for patients with stable chronic obstructive pulmonary disease (COPD). *Cochrane Database of Systematic Reviews* 2017, Issue 8. Art. No.: CD012748. DOI: 10.1002/14651858.CD012748.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To compare the efficacy and safety of adding oral theophylline or doxofylline to usual treatment (long-acting beta$_2$-agonists, antimuscarinics, inhaled corticosteroids) versus providing usual treatment alone for patients with stable COPD.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable condition that is characterised by persistent, usually progressive, airflow limitation; spirometry is required to make the diagnosis, and the presence of a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio < 0.70 confirms its presence, which is associated with chronic respiratory symptoms such as dyspnoea, chronic cough, sputum production, wheezing, and chest tightness (GOLD 2017). COPD is associated with significant mortality and morbidity and is the fourth leading cause of death worldwide (WHO 2012). Reported prevalence data vary widely around the world. The Burden of Obstructive Lung Diseases study (BOLD) reported prevalence of COPD severity grade 2 or higher of 10.1% (standard error (SE) 4.8) (BOLD 2007), and prevalence estimated in the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) ranged from a low of 7.8% in Mexico City to a high of 19.7% in Montevideo (Uruguay) (PLATINO).

Worldwide, the main cause of COPD is tobacco smoking, but other risk factors include air pollution, burning of biomass, and occupational exposure (Eisner 2010).

Clinicians commonly use various pharmacological treatments in COPD management to relieve symptoms, enhance exercise tolerance, improve quality of life, and prevent and treat exacerbations.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

No pharmacological treatment has had a clear effect in lowering mortality among patients with COPD (GOLD 2017).

The natural history of COPD is characterised by exacerbations or episodes of clinical and lung function deterioration associated with an increase in airway and systemic inflammation. Exacerbations accelerate lung function decline, reduce physical activity, diminish quality of life, increase risk of dying, and are considered the main prognostic factor for future exacerbations; consequently, appropriate pharmacological management of the disease is important for reducing and preventing exacerbations while controlling symptoms (Hurst 2010).

Description of the intervention

Guidelines for COPD management recommend treatment based on disease severity, which should be determined by assessing the degree of bronchial obstruction and the presence and frequency of exacerbations and symptoms such as dyspnoea (COPD-X 2016; GOLD 2017). Bronchodilators are considered the main strategy in the pharmacological management of COPD; short-acting bronchodilators (beta$_2$-agonists and anticholinergics) are given as the first pharmacological step in treating patients with COPD, and long-acting bronchodilators can be introduced in more symptomatic patients with a history of exacerbations or greater functional impact (COPD-X 2016; GOLD 2017; NICE 2010).

Guidelines include contradictory recommendations regarding use of oral xanthine derivatives such as theophylline or doxophylline based on their narrow safety margin and questionable effectiveness. National Institute for Health and Care Excellence (NICE) recommendations stating that theophylline should be used only after a trial of short-acting bronchodilators and long-acting bronchodilators, or in patients who are unable to use inhaled therapy (NICE 2010), contrast with GOLD (Global Initiative for Obstructive Lung Disease) guidelines, which consider that theophylline exerts a small bronchodilator effect only in patients with stable COPD, achieving modest symptomatic benefits, and do not include theophylline in the pharmacological treatment algorithm (GOLD 2017).

Previously published systematic reviews on this topic show evidence of improvement in lung function but no evidence of an effect on outcomes such as exacerbation, rate of hospitalisation, or quality of life (Molfino N 2006; Ram 2009). However, theophylline remains one of the most widely prescribed drugs for COPD treatment worldwide (Barnes 2013).

How the intervention might work

Besides bronchodilation, use of xanthines leads to effects such as anti-inflammatory activity and improved diaphragm contractility, but their clinical relevance has not been firmly established (Barnes 2013; Spina 2016).

Several mechanisms underlying these effects have been proposed but remain poorly understood. In high concentrations, theophylline is a weak non-selective inhibitor of phosphodiesterase (PDE) isoenzymes. Theophylline antagonises adenosine A_1 and A_2 receptors, and increases interleukin-10, which has a broad spectrum of anti-inflammatory effects; in low therapeutic concentrations, theophylline activates histone deacetylase (HDAC)-2 activity. Other molecular effects include activation of ryanodine receptors, and of the cystic fibrosis transmembrane conductance regulator (CFTR), and inhibition of phosphoinositide 3-kinase, inhibition of poly(ADP-ribose)polymerase-1 (PARP-1), and activation of small and intermediate conductance calcium-activated potassium channels (Barnes 2013).

Major side effects associated with theophylline occur when plasma concentrations rise above 20 μg/mL; these include gastrointestinal side effects (vomiting, diarrhoea, and nausea). At concentrations greater than 30 μg/mL, the potential for cardiac arrhythmia (A_1 receptor antagonism), hypotension, hypokalaemia, and hyperglycaemia is greater (Spina 2016).

Doxofylline is a xanthine derivative that exhibits both bronchodilator and anti-inflammatory activity (Spina 2016). A recent pharmacological study showed that doxofylline does not directly inhibit any HDAC enzymes nor any PDE enzyme subtypes, nor does it act as an antagonist at any of the known adenosine receptors; this may explain the improved safety profile of doxofylline versus theophylline (Van Mastbergen 2012).

Why it is important to do this review

Use of oral xanthine derivatives for treatment of COPD continues to be a controversial topic, owing to low clinical effectiveness, high frequency of adverse effects and drug interactions, and the availability of new inhaled bronchodilators and oral anti-inflammatory drugs with adequate evidence of effectiveness (GOLD 2017).

However, theophylline, which has been available since 1937 for treatment of lung disease, is still one of the most widely prescribed drugs worldwide for COPD treatment.

In most treatment guidelines, the xanthines have now been consigned to second- or third-line therapy because of their narrow therapeutic window and propensity for pharmacological interactions (Spina 2016). Recent evidence from observational studies indicates that theophylline slightly increases all-cause death among patients with COPD (Horita 2015); this could further limit its use. Findings of this review will be important for determining the balance between risks and benefits.

As an additional option, doxofylline has recently shown potentially lower risk of adverse events when compared with theophylline; doxofylline is presently used in some regions of the world and could offer an alternative treatment.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

OBJECTIVES

To compare the efficacy and safety of adding oral theophylline or doxofylline to usual treatment (long-acting beta$_2$-agonists, antimuscarinics, inhaled corticosteroids) versus providing usual treatment alone for patients with stable COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We will include double-blind placebo-controlled trials and open trials including no placebo (usual treatment group) that were conducted in patients with stable COPD who received the trial treatment for at least 12 weeks. We will include studies reported in full text, as well as those published as abstract only and reported as unpublished data.

In the light of increased risk of mortality described recently in the literature as an undesirable effect associated with long-term use of theophylline (Horita 2015), we will include long-term follow-up observational studies such as analytical cohort studies comparing the addition of theophylline or doxofylline to usual treatment versus usual treatment alone.

Types of participants

We will include adults with a diagnosis of stable COPD (mild, moderate, severe, very severe). We will include only studies that use an accepted set of criteria to screen participants for this condition (i.e. guidelines of the American Thoracic Society (ATS); the British Thoracic Society (BTS); Global Initiative for Obstructive Lung Disease (GOLD) 2016; and the Thoracic Society of Australia and New Zealand (TSANZ)).

Types of interventions

We will include studies comparing the following interventions in which the "intervention group" is receiving xanthine derivatives as complementary therapy to previously established therapies with any of the following active treatments for disease control: long-acting beta-agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and/or inhaled corticosteroids (ICSs).

In keeping with currently accepted COPD guidelines, we will include the following comparisons.

1. LABA + ICS therapy vs LABA + ICS therapy + xanthine (theophylline or doxofylline).
2. LAMA therapy vs LAMA + xanthine (theophylline or doxofylline).
3. LAMA + LABA + ICS therapy vs LAMA + LABA + ICS + xanthine (theophylline or doxofylline).
4. LABA + LAMA therapy vs LABA + LAMA + xanthine (theophylline or doxofylline).

Types of outcome measures

Primary outcomes

1. Acute exacerbations of COPD, defined as the need for treatment with oral steroids, antibiotics, or both (moderate exacerbations), or hospital admission for a COPD exacerbation (severe exacerbations)
2. Health-related quality of life (measured by a generic or disease-specific tool)
3. Mortality (all-cause)

Secondary outcomes

1. Dyspnoea scores: defined by the modified Medical Research Council (mMRC), the Chronic Respiratory Questionnaire Self-Administered Standardized (CRQ-SAS) dyspnoea domain, or scores on the Baseline Dyspnoea Index (BDI)-Transition Dyspnoea Index (TDI)
2. Lung function: change from baseline in trough FEV_1
3. Exercise capacity: six-minute walking test
4. Serious adverse events/non-fatal (gastrointestinal and cardiovascular) events

Search methods for identification of studies

Electronic searches

We will identify randomised controlled trials (RCTs) from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (http://crso.cochrane.org/).
2. Weekly searches of MEDLINE Ovid SP.
3. Weekly searches of Embase Ovid SP.
4. Monthly searches of PsycINFO Ovid SP.
5. Monthly searches of the Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO.
6. Monthly searches of the Allied and Complementary Medicine Database (AMED) EBSCO.
7. Handsearches of the proceedings of major respiratory conferences.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Review authors identified studies contained in the Trials Register by using search strategies based on the scope of Cochrane Airways. We have provided details of these strategies, as well as a list of hand-searched conference proceedings, in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We will also search the following trials registries.

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (https://www.clinicaltrials.gov/).
2. World Health Organization International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/).

To identify long-term follow-up observational studies, we will carry out additional searches of MEDLINE, Embase, and CINAHL. We have provided the MEDLINE search strategy in Appendix 3 and will adapt this strategy appropriately for use in searching the other databases.

We will search all sources from inception to present, with no restriction on language or type of publication.

Searching other resources

We will identify trials by using the Latin American Caribbean Health Sciences Literature (LILACS)/BIREME database.

We will check the reference lists of all primary studies and review articles for additional references and will search relevant manufacturers' websites for study information.

We will search for errata or retractions from included studies published in full text on PubMed and will report within the review the date this was done.

Data collection and analysis

Selection of studies

Two review authors (OMG and MXR) will screen the titles and abstracts of search results independently and will code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies; two review authors (RD and OMG) will independently screen them for inclusion and will record reasons for exclusion of ineligible studies. We will resolve disagreements through discussion, or, if required, we will consult a third review author (MXR). We will identify and exclude duplicates and will collate multiple reports of the same study, so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form that has been piloted on at least one study included in the review to document study characteristics and outcome data. Two review authors (OMG and MXR) will extract the following study characteristics from included studies.

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

Two review authors (OMG and MXR) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a useable way. We will resolve disagreements by consensus or by consultation with a third review author (RD). One review author (OMG) will transfer data into the Review Manager file (RevMan 2014). We will double-check that data have been entered correctly by comparing data presented in the systematic review versus those included in study reports. A second review author (MXR) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (RD and OMG) will assess risk of bias independently for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve disagreements by discussion or by consultation with another review author (MXR). We will assess risk of bias according to the following domains.

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

We will judge each potential source of bias as introducing high, low, or unclear risk, and will provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). When information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

When considering treatment effects, we will take into account the risk of bias for studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and will justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data (such as mortality, hospital admissions, numbers of participants with one or more exacerbations) as odds ratios (ORs). If data on exacerbations are reported as time free of exacerbation or time to first exacerbation, we will use the hazard ratio. If rates of exacerbation are reported, we will analyse these using rate ratios. We will report all measures of treatment effect with corresponding 95% confidence intervals (CIs).

We will analyse continuous outcome data (such as quality of life scores and FEV_1 measurements) as mean differences (MDs). To compare effects of treatment on respiratory health-related quality of life (HRQoL) as reported on different scales (e.g. Chronic Respiratory Questionnaire (CRQ), St George's Respiratory Questionnaire (SGRQ)), we will standardise study results to a uniform scale. Once we have completed this step for all studies reporting quality of life outcomes, we will conduct a meta-analysis (if appropriate) to obtain standardised mean differences.

We will undertake meta-analyses only when this is meaningful, that is, when treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. When multiple trial arms are reported in a single study, we will include only the relevant arms.

We will use intention-to-treat (ITT) or 'full analysis set' analyses when reported, instead of complete or per-protocol analyses.

For outcomes reported at different follow-up periods, we will consider inclusion of three stratified analyses: three-month follow-up; six-month follow-up; and 12-month follow-up.

Unit of analysis issues

For safety outcomes, we will include a numerical rating scale (NRS) for estimation of long-term adverse events and of fatal (mortality) and non-fatal (gastrointestinal and cardiovascular) events.

If we find enough information on non-fatal outcomes, we will present the number of events per participant (i.e. number of gastrointestinal and cardiovascular events) as continuous data, using the summary of events reported for the same participant at one-year follow-up. Otherwise, we will present dichotomous data using participants (rather than events) as the unit of analysis to avoid counting the same participant more than once.

We will pay special attention to the ways that adverse events are labelled (i.e. as single events or included in a group of similar events (e.g. nausea, vomiting, gastrointestinal symptoms)) to avoid double-counting of same events.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible. If this is not possible, and missing data are thought to introduce serious bias, we will take this into consideration when performing GRADE assessment of the quality of evidence for those affected outcomes.

Assessment of heterogeneity

We will evaluate possible sources of clinical heterogeneity (i.e. whether treatments, participants, and the underlying clinical question are similar enough among trials). If we identify substantial clinical heterogeneity, we will consider reporting by subgroups.

We will use the I^2 statistic to measure statistical heterogeneity among trials included in each analysis. In cases of unexplained statistical heterogeneity, we will present results independently (i.e. unpooled).

Assessment of reporting biases

We will assess possible reporting bias on two levels: within-study bias and between-study bias.

We will examine within-study selective outcome reporting as part of the overall 'Risk of bias' assessment. We will attempt to find protocols for included studies and will compare outcomes stated in the protocols with those reported in the publications. If protocols cannot be found, we will compare outcomes listed in the methods section of a publication versus those for which results are reported. We will contact study authors for clarification if we identify indications of reporting bias.

We will create a funnel plot of effect estimates against standard errors (SEs) to assess possible between-study reporting bias if we include at least 10 studies in the review. We will consider possible explanations if we note asymmetry of the funnel plot.

Data synthesis

We will present independent pooled results for the four comparisons presented under Types of interventions. We will use a fixed-effect model and will perform a sensitivity analysis using a random-effects model.

We will present in 'Summary of findings' tables results of data synthesised for each of the critical and important review outcomes according to the GRADE approach, as described in the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 11. We will use the GRADE profiler to construct tables based on each comparison for the subgroup

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Type of xanthine used in the treatment group (theophyline or doxophylline). Despite similar mechanisms of action, data have shown differences in the safety profiles of these agents.

Quality of evidence

For the 2017 update, we will use the GRADE approach, as outlined in the *GRADE Handbook* (Schünemann 2017), to assess the quality of evidence for the following (clinically relevant) outcomes: acute exacerbations of COPD, quality of life, mortality, dyspnoea scores, lung function, exercise capacity, and serious adverse events. Two review authors (OMG and RD) will independently assess the quality of evidence for each of the outcomes above. We will consider evidence from RCTs as high quality and will downgrade evidence by one level for serious (or two levels for very serious) limitations, based on the following: design (risk of bias); consistency across studies; directness of evidence; precision of estimates; and presence of publication bias. We will use the GRADEpro-GDT 2013 (GRADEpro GDT) Guideline Development Tool to create a 'Summary of findings' table to report the quality of evidence.
For safety outcomes based on the NRS, we will consider evidence as low quality but will upgrade the evidence one level for Guyatt 2011 for the following reasons.

1. Large magnitude of effect (direct evidence, risk ratio (RR) 2 to 5, or RR 0.5 to 0.2, with no plausible confounders), or very large magnitude of effect (RR > 5, or RR < 0.2, with no serious problems with risk of bias or precision).
2. Dose-response gradient.
3. Demonstrated effect reduced by all plausible residual confounders or biases, or suggestion of a spurious effect when results show no effect.

For outcomes reported by RCTs and on an NRS (i.e. mortality), we will assess the quality of evidence by applying GRADE recommendations.(Schünemann 2013). The GRADE approach yields an assessment of the quality of a body of evidence according to one of four grades.

1. High: We are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
4. Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

Comparison I. Studies that compared effects of LABA + ICS therapy vs LABA + ICS therapy + xanthine (theophylline or doxofylline) in patients with stable COPD

1. Studies that evaluated the addition of theophylline
2. Studies that evaluated the addition of doxofylline

Comparison 2. Studies that compared effects of LAMA therapy vs LAMA + xanthine (theophylline or doxofylline) in patients with stable COPD

1. Studies that evaluated the addition of theophylline
2. Studies that evaluated the addition of doxofylline

Comparison 3. Studies that compared effects of LAMA + LABA + ICS therapy vs LAMA + LABA + ICS + xanthine (theophylline or doxofylline) in patients with stable COPD

1. Studies that evaluated the addition of theophylline
2. Studies that evaluated the addition of doxofylline

Comparison 4. Studies that compared effects of LABA + LAMA therapy vs LABA + LAMA + xanthine (theophylline or doxofylline) in patients with stable COPD

1. Studies that evaluated the addition of theophylline
2. Studies that evaluated the addition of doxofylline

If substantial or considerable unexplained heterogeneity (> 60%) is present, we will not perform meta-analysis.
If information is available on disease severity of the population in included studies, we will look for differences in the treatment effect. If we find significant differences, we will consider conducting a post hoc subgroup analysis by COPD severity (mild, moderate, and severe).
If information is available on high versus low doses of theophylline in included studies, we will look for differences in the treatment effect by performing comparisons that include use of corticosteroids (LABA + ICS vs LABA + ICS + theophylline and LAMA + LABA + ICS vs LAMA + LABA + ICS + theophylline). If we find significant differences, we will consider conducting a post hoc subgroup analysis by dosage of theophylline and concomitant use of corticosteroids.
We will perform the formal test for subgroup interactions provided in Review Manager (RevMan 2014).

Sensitivity analysis

We plan to carry out the following sensitivity analyses after removing them from primary outcome analyses.

1. Comparison based on our 'Risk of bias' assessment of included studies. We will exclude studies at high risk of selection bias.
2. Comparison of results from a fixed-effect model versus results from a random-effects model.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ACKNOWLEDGEMENTS

Chris Cates served as the Editor and commented critically on this protocol.

The Background and Methods sections of this protocol are based on a standard template used by Cochrane Airways.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Airways. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health.

Professors Olga Milena Garcí a Morales, Marí a Ximena Rojas-Reyes and Rodolfo J. Dennis thank professor Carlos Celis, who commented the background.

REFERENCES

Additional references

Barnes 2013
Barnes P. Theophylline. *American Journal of Respiratory and Critical Care Medicine* 2013;**188**(8):901–6.

BOLD 2007
Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. *Lancet* 2007;**370**(9589):741–50. [DOI: 10.1016/S0140-6736(07)61377-4]

COPD-X 2016
Yang IA, Dabscheck E, George J, Jenkins S, McDonald CF, McDonald V, et al. The COPD-X Plan: Australian and New Zealand guidelines for the management of chronic obstructive pulmonary disease 2016. http://copdx.org.au/copd-x-plan/ (accessed 27 January 2016).

Eisner 2010
Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 2010;**182**(5):693–718. [DOI: 10.1164/rccm.200811-1757ST]

GOLD 2017
Global Initiative for Chronic Obstructive Lung Disease (GOLD). From the global strategy for the diagnosis, management and prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. www.goldcopd.org/ (accessed 27 January 2017).

GRADEpro GDT [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed 27 January 2017. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Guyatt 2011
Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(12):1311–6. [DOI: http://dx.doi.org/10.1016/j.jclinepi.2011.06.004]

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Horita 2015
Horita N, Miyazawa N, Kojima R, Inoue M, Ishigatsubo Y, Kaneko T. Chronic use of theophylline and mortality in chronic obstructive pulmonary disease: a meta-analysis [Uso crónico de teofilina y mortalidad en la enfermedad pulmonar obstructiva crónica: un metaanálisis]. *Archivos de Bronconeumología* 2016;**52**(5):233–8. [DOI: 10.1016/j.arbres.2015.02.021]

Hurst 2010
Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *New England Journal of Medicine* 2010;**363**(12):1128–38. [DOI: 10.1056/NEJMoa0909883]

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):e1000097. [DOI: 10.1371/journal.pmed.1000097]

Molfino N 2006
Molfino N, Zhang P. A meta-analysis on the efficacy of oral theophylline in patients with stable COPD. *International Journal of COPD* 2006;**1**(3):261-6.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

NICE 2010
National Clinical Guideline Center. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. https://www.nice.org.uk/guidance/cg101 (accessed 27 January 2017).

PLATINO
Menezes AM, Perez-Padilla R, Jardim JR, Muiño A, Lopez MV, Valdivia G, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet* 2005;**366**(9500):1875–81. [DOI: 10.1016/S0140-6736(05)67632-5]

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schünemann 2013
Schünemann H, Tugwell P, Reeves B, Akl EA, Santesso N, Spencer FA. Non-randomized studies as a source of complementary, sequential or replacement evidence for randomized controlled trials in systematic reviews on the effects of interventions. *Research Synthesis Methods* 2013;**4**: 49–62. [DOI: 10.1002/jrsm.1078]

Schünemann 2017
Schu¨ nemann H, Brozek J, Guyatt G, Oxman A. Handbook for Grading the Quality of Evidence and the Strength of Recommendations Using the GRADE Approach. http://gdt.guidelinedevelopment.org/app/handbook/handbook.html (accessed 27 January 2017).

Spina 2016
Spina D, Page CP. Xanthines and phosphodiesterase inhibitors. *Handbook of Experimental Pharmacology*. 1. Vol. **15**, Springer Berlin Heidelberg, 2016:1–29. [DOI: 10.1007/164_2016_71]

Van Mastbergen 2012
Van Mastbergen J, Jolas T, Allegra L, Page CP. The mechanism of action of doxofylline is unrelated to HDAC inhibition, PDE inhibition or adenosine receptor antagonism. *Pulmonary Pharmacology and Therapeutics* 2012;**25**(1):55–61. [10.1016/j.pupt.2011.10.007]

WHO 2012
World Health Organization. WHO global report: mortality attributable to tobacco. http://www.who.int/tobacco/publications/surveillance/rep_mortality_attributable/en/ (accessed 27 January 2017).

References to other published versions of this review

Ram 2009
Ram FSF, Jones P, Jardim J, Castro AA, Atallah A
˙ N, Lacasse Y, et al. Oral theophylline for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: 10.1002/14651858.CD003902]

* *Indicates the major publication for the study*

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

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

MEDLINE search strategy used to identify trials from the CAGR

COPD search

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

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Filter used to identify RCTs

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

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

Appendix 2. Search strategy used to identify RCTs from the Airways Trials Register

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2 MeSH DESCRIPTOR Bronchitis, Chronic
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4 COPD:MISC1
#5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 MeSH DESCRIPTOR Theophylline
#8 MeSH DESCRIPTOR Xanthines
#9 *methylxanthine
#10 theophylline*
#11 Doxofylline or doxophylline
#12 #7 OR #8 OR #9 OR #10 OR #11
#13 #6 AND #12

Appendix 3. Search strategy used to identify observational studies

MEDLINE Ovid SP

1. exp Pulmonary Disease, Chronic Obstructive/
2. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw.
3. (COPD or COAD or COBD or AECOPD).tw.
4. or/1-3
5. Theophylline/
6. Xanthines/
7. methylxanthine$.tw.
8. theophylline$.tw.
9. (doxofylline$ or doxophylline$).tw.
10. or/5-9
11. 4 and 10
12. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/
13. (cohort or longitudinal or prospective).ti,ab.
14. 12 or 13
15. 11 and 14

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

CONTRIBUTIONS OF AUTHORS

Olga Milena Garcia and Maria Ximena Rojas wrote the first draft of the protocol. Rodolfo Dennis commented on and contributed to the protocol and approved it before publication.

DECLARATIONS OF INTEREST

Over the past two years, RD has participated in advisory boards and in continued medical education activities sponsored by pharmaceutical industry entities interested in the treatment of patients with COPD, and has received payment for these activities.

OMG has no conflict of interest in the present review.

MXR has no conflict of interest in the present review.

SOURCES OF SUPPORT

Internal sources

- Mari´ a Ximena Rojas and Rodolfo Dennis, Colombia.

Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine of the Pontificia Universidad Javeriana, supported the time dedicated by review authors.

External sources

- No sources of support supplied

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.