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Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD012621.
DOI: 10.1002/14651858.CD012621.

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[Intervention Protocol]

Phosphodiesterase 5 inhibitors for pulmonary hypertension

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Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 4, 2017.

Citation: Barnes H, Brown Z, Burns A, Williams T. Phosphodiesterase 5 inhibitors for pulmonary hypertension. *Cochrane Database of Systematic Reviews* 2017, Issue 4. Art. No.: CD012621. DOI: 10.1002/14651858.CD012621.

ABSTRACT

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

To determine the efficacy of PDE-5 inhibitors for pulmonary hypertension in adults and children.

BACKGROUND

Description of the condition

Pulmonary hypertension (defined as a mean pulmonary artery pressure ≥ 25 mmHg at rest on right-heart catheterisation) comprises a complex group of conditions characterised by increased pulmonary vascular resistance, which ultimately leads to right-heart failure (McLaughlin 2009).

Increased pulmonary vascular resistance is caused by vascular remodelling and thickening in the small- and medium-sized arterioles, fibrinoid necrosis, the formation of eccentric, concentric, or plexiform lesions, and the loss of vascular tone. This process of cellular hypertrophy and hyperplasia is mediated by intracellular calcium and protein kinase C, inflammatory cytokines, and altered energy metabolism. Remodelling and vasoconstriction lead to hypoxia, causing further vasoconstriction and further hypoxia (Guignabert 2013; Sim 2010).

Pulmonary hypertension is classified into five groups of multiple clinical conditions grouped according to similar clinical presentations and pathophysiological and haemodynamic characteristics, with distinct treatment strategies for each group. Group 1 pulmonary arterial hypertension (PAH) includes idiopathic and heritable PAH and PAH due to pathology of the small pulmonary arterioles resulting from connective tissue disorders, drugs or toxins, and portal hypertension. Pulmonary arterial hypertension is caused by increased pulmonary vascular resistance due to occlusive vasculopathy of the small pulmonary arteries and arterioles. Pulmonary arterial hypertension is a rare disease, with an estimated prevalence of 10 to 52 cases per million (Ling 2012; Peacock 2007). However, screening for pulmonary hypertension for all causes demonstrates a prevalence of 320 cases per 100,000 (Strange 2012).

Group 2 consists of pulmonary hypertension due to left-heart disease, caused by increased flow through the pulmonary vasculature (e.g. congenital cardiac defects or portal hypertension), or increased pulmonary pressures (e.g. mitral valve disease, left ventricular disease, and constrictive myopathies). Group 3 comprises pulmonary hypertension as a result of lung diseases or hypoxia, or both caused by a decrease in the area of the pulmonary vascular bed (e.g. pulmonary emboli, interstitial lung disease), or conditions that induce hypoxic vascoconstriction. Group 4 refers to

cases of pulmonary hypertension due to chronic thromboembolic occlusion of pulmonary vasculature, and Group 5 consists of cases of pulmonary hypertension due to unclear and/or multifactorial mechanisms including haematological, systemic, or metabolic disorders (McLaughlin 2009).

People with pulmonary hypertension often present with symptoms of dyspnoea, fatigue, syncope, and right-heart failure (Galie 2016). Right-heart catheterisation remains the gold standard of diagnosis to confirm pulmonary hypertension and to further investigate potential causes and treatment targets. Pulmonary arterial hypertension is defined as a mean pulmonary artery pressure greater than 25 mmHg; a pulmonary capillary wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure less than or equal to 15 mmHg; and a pulmonary vascular resistance greater than 3 Wood units (Galie 2016). Elevation of the pulmonary capillary wedge pressure suggests pulmonary hypertension secondary to left-heart disease. People with confirmed PAH should undergo acute vasodilator testing to assess for pulmonary vasoreactivity, thus being suitable for long-term calcium channel blocker therapy (McLaughlin 2009).

Following history, examination, electrocardiogram, echocardiogram, chest X-ray, and right-heart catheter, other investigations for people with pulmonary hypertension should include pulmonary function tests and high-resolution computed tomography chest to assess for underlying lung disease, ventilation/perfusion scan to assess for chronic thromboembolic pulmonary hypertension, thyroid function tests, autoimmune serology, HIV and hepatitis screening to assess for underlying aetiologies, and a six-minute walk test or exercise testing, biomarkers to monitor response to treatment and for prognostication (Galie 2016).

The natural history and prognosis of pulmonary hypertension varies amongst the groups, however it remains a progressive and often fatal condition. Predictors of poor prognosis include advanced New York Heart Association (NYHA) functional class, poor performance in six-minute walk test, high right atrial pressure, significant right ventricular dysfunction, evidence of right ventricular failure, and low cardiac index (Thenappan 2007).

Description of the intervention

Recent years have seen the introduction of evolving therapies for pulmonary hypertension, with an improvement in the one-year survival rate to 84% from 68% in the 1980s (Archer 2009). The goals of therapy are to achieve a state associated with good quality of life and exercise tolerance with low mortality risk and to maintain right ventricular function, using supplemental oxygen and treatment of the underlying cause. The underlying pulmonary artery endothelial dysfunction in Group 1 PAH enables the use of PAH-specific targeted treatments promoting vasorelaxation and suppression of cellular proliferation within the pulmonary artery wall, including nitric oxide and phosphodiesterase type 5 inhibitors, prostanoids, endothelin receptor antagonists, and calcium channel blockers (McLaughlin 2009).

How the intervention might work

Nitric oxide performs as a pulmonary vasodilator by activating soluble guanylate cyclase, stimulating the production of cyclic guanosine monophosphate (cGMP), which in turn activates myosin light chain phosphatase, which reduces phosphorylation of myosin to reduce pulmonary vascular tone. Increased intracellular cGMP also inhibits calcium entry, thereby reducing intracellular calcium leading to less hypertrophy and hyperplasia, as well as antiproliferative and pro-apoptotic effects that may reverse pulmonary artery remodelling. Nitric oxide also inhibits platelet recruitment, adhesion, and aggregation (Sim 2010).

However, nitric oxide administration is not without risk. High levels of inhaled nitric oxide may lead to oxidative stress and cause tissue damage, reperfusion injury, and a pulmonary inflammatory reaction. Inhaled nitric oxide is rapidly absorbed into the blood stream, where it is converted to methaemoglobin, leading to impaired rather than improved oxygen delivery (Sim 2010).

Phosphodiesterase type 5 (PDE-5) specifically reduces cGMP degrading enzyme activity, thereby increasing cGMP production. Phosphodiesterase type 5 inhibitors are not thought to induce the same levels of oxidation as inhaled nitric oxide (Ghofrani 2004). Phosphodiesterase type 5 inhibitors that have been investigated for use in Group 1 PAH include sildenafil, tadalafil, and vardenafil. These agents have been shown in clinical trials to improve six-minute walk distance and haemodynamics (Archer 2009; Galie 2016; McLaughlin 2009).

The data is less clear in non-Group 1 PAH patients, in whom this class of drug may be potentially harmful. There are different mechanical and functional factors at play leading to the development of pulmonary hypertension in these patients, including increased pulmonary pressures and a decrease in the pulmonary vascular bed area, which may not necessarily be improved by PDE-5 inhibitors. Phosphodiesterase type 5 inhibitors may theoretically improve function in Group 2 patients with left-heart disease. Previous studies in heart failure patients have demonstrated that nitric oxide is responsible for regulation of vascular tone, and infusion of NG-monomethyl-L-arginine, an inhibitor of nitric oxide synthase, caused less vasoconstriction in heart failure patients compared to those with a normal pulmonary vascular resistance (Cooper 1996). Trials using sildenafil in Group 2 pulmonary hypertension patients have shown some evidence of improvement in exercise capacity, ventilation efficiency, and quality of life (Lewis 2007). However, other studies have demonstrated unbalanced pulmonary dilatation as a consequence of nitric oxide and analogues may lead to increased preload due to a poorly compliant left ventricle, and therefore a significant increase in pulmonary capillary wedge pressure, which may even precipitate acute pulmonary oedema (Bocchi 1994).

Furthermore, trials using other PAH-specific therapies including epoprostenol and endothelin receptor antagonists in people with Group 2 pulmonary hypertension demonstrated an increased risk of hospitalisations, disease progression, and hypoxaemia. People with left ventricular dysfunction may not be able to tolerate the increased flow across a newly dilated pulmonary vascular bed (Guazzi 2012).

People with Group 3 chronic lung diseases may experience worsening ventilation perfusion mismatch and increased hypoxaemia. A study in people with pulmonary hypertension associated with chronic obstructive pulmonary disease demonstrated an improvement in pulmonary artery pressures, but at the cost of worsening arterial oxygenation (Blanco 2010).

Why it is important to do this review

Given recent advancements in the understanding of the pathophysiological mechanisms and treatments for pulmonary hypertension with significant contributions in the area in the last decade, we intend to summarise the current evidence relating to the use of PDE-5 inhibitors in pulmonary hypertension.

This review will aim to quantify any potential benefit for PDE-5 inhibitors in people with PAH in terms of haemodynamic measurements and patient-centred outcomes, and balance this against any potential treatment harms, in order to guide patient preference, clinician treatment choices, and guidelines for policymakers. This review will also examine the available evidence to determine whether there is any potential benefit or harm in using PDE-5 inhibitors in people with Group 2 to 5 pulmonary hypertension. This review builds on a previous review (Kanthapillai 2004), since which further concepts regarding pathophysiology have been developed, and a number of more recent randomised controlled trials using PDE-5 inhibitors have been published.

OBJECTIVES

To determine the efficacy of PDE-5 inhibitors for pulmonary hypertension in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

We will include single- or double-blinded randomised controlled trials in which PDE-5 inhibitors are compared to placebo or any other treatment. We will define 'randomised' as studies described by the author as 'randomised' anywhere in the manuscript. All trials defined as such, published or unpublished, in any language, will be potentially eligible for inclusion.

Types of participants

We will include any individual with a diagnosis of pulmonary hypertension from any cause who requires medical treatment for their condition. We will define pulmonary hypertension according to accepted criteria (Galie 2016; McLaughlin 2009).

Comparison 1 will specifically assess the effects of PDE-5 inhibitors on Group 1 PAH confirmed as a mean pulmonary artery pressure > 25 mmHg by right-heart catheterisation. Comparison 2 will include Group 2 to 5 pulmonary hypertension participants with a diagnosis of pulmonary hypertension as defined by the authors.

We will specify subgroups of adults older than 18 years and a paediatric population younger than 18 years.

Types of interventions

We will include studies comparing any type of PDE-5 inhibitors by any route of administration with placebo or any other treatment used for pulmonary hypertension. We will include all PDE-5 inhibitors as a total class in the intervention arm and then perform subgroup analyses to compare different PDE-5 inhibitors separately. If multiple doses are used, we will perform subgroup analyses by dose. In the control arm, we will include usual care, placebo, and other treatments for pulmonary hypertension as separate comparisons. We will include studies with co-interventions provided they are not part of the randomised treatment. Where indicated, we will perform subgroup analyses depending on the co-interventions used. If studies are too heterogenous for meta-analyses, we will describe them in narrative form.

Types of outcome measures

Primary outcomes

1. Change in NYHA functional class
2. Six-minute walk distance
3. Mortality

Secondary outcomes

1. Haemodynamic parameters including change in mean pulmonary artery pressure, change in cardiac output, cardiac index
2. Exercise capacity other than six-minute walk distance
3. Quality of life/health status, by any validated scale

4. Dyspnoea score, including visual analogue scale or Borg scale
5. Hospitalisation/intervention
6. Adverse events

Reporting one or more of the outcomes listed here in the study is not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will identify trials from searches of the following databases:

- The Cochrane Airways Group Register of Trials;
- Cochrane Central Register of Controlled Trials (CENTRAL) through the Cochrane Register of Studies Online (crso.cochrane.org);
- MEDLINE (Ovid) 1950 to date;
- Embase (Ovid) 1974 to date;
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

The proposed MEDLINE strategy is provided in Appendix 1. We will adapt this for use in the other databases. All databases will be searched from their inception to the present, and there will be no restriction on language of publication. We will search for handsearched conference abstracts and grey literature through the CENTRAL database.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will handsearch reference lists of included studies, relevant chapters, and review articles. We will use Google to search for grey literature and conference abstracts. We will translate any relevant article into English for potential inclusion. Where data are missing, we will attempt to contact the trial investigators.

Data collection and analysis

Selection of studies

Two review authors (HB, ZB) will independently screen all abstracts to determine if they meet the inclusion criteria for the review. We will seek full-text publications for those papers that possibly or definitely meet the inclusion criteria. Two review authors will then independently review all full-text articles to determine eligibility, recording reasons for ineligibility of those that do not. Any disagreements will be resolved through discussion, or, if required, by seeking consensus from a third review author (AB). We plan to include a PRISMA study flow diagram in the full review to document the screening process and will include a 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

Two review authors (HB and ZB) will independently extract data from included studies, and where appropriate, will pool data in the Cochrane statistical software Review Manager 5 for further analysis (RevMan 2014). We will use a data collection form that we plan to pilot on one study for inclusion in the review, containing the following data.

- Methods: study design, duration, study setting, date of study
- Participants: number, mean age and age range, gender, inclusion and exclusion criteria
- Intervention: type of PDE-5 inhibitor, dose, mode of administration, control drug, co-interventions, and exclusions
- Outcomes: primary and secondary outcomes as specified, type of scale used, time points collected
- Risk of bias summary
- Other: funding for trial, any conflicts of interest for trial authors

Assessment of risk of bias in included studies

Two review authors (HB, ZB) will independently assess the included studies for risk of bias using the Cochrane tool for assessment of risk of bias (Higgins 2011). We will assess the following domains.

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

We will judge each potential source of bias as low risk, unclear risk (insufficient information to form a judgement), or high risk, and provide justification with evidence from each trial in the 'Risk of bias' table. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

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

Measures of treatment effect

Where possible, we will pool and present results from dichotomous data as odds ratio (OR). Where possible, we will present results from continuous variables using a fixed-effect model and calculate the mean differences (MD) or standardised mean differences (SMD) where scales are combined, with the 95% confidence intervals (95% CI). If data from rating scales are combined in a meta-analysis, we will ensure that they are entered with a consistent direction of effect (e.g. lower scores always indicate improvement). If both change from baseline and endpoint scores are available for continuous data, we will use change from baseline scores where possible. If outcomes are reported at multiple time points, we will consistently extract and include the latest reported time point but will consider outcomes reported at other time points. We will only combine data reported at different time points if this is clinically appropriate.

We will describe skewed data narratively (e.g. as medians and interquartile ranges for each group).

We will use intention-to-treat or 'full analysis set' analyses where they are reported (i.e. those where data have been imputed for participants who were randomly assigned but did not complete the study) instead of completer or per-protocol analyses.

Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of children admitted to hospital, rather than number of admissions per child). However, if rate ratios are reported in a study, we will analyse them on this basis. We will only meta-analyse data from cluster-randomised controlled trials if the available data have been adjusted (or can be adjusted) to account for the clustering.

Dealing with missing data

We will contact investigators in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

For pooled analyses we will quantify statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across trials due to heterogeneity rather than sampling error. We will consider significant statistical heterogeneity to be present if the $I^2$is greater than 50%. Where we identify significant heterogeneity, we will explore possible causes using prespecified subgroup analyses.

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

'Summary of findings' table

We will create a 'Summary of findings' table that will include NYHA functional class status, quality of life, mortality, change in haemodynamics, and six-minute walk distance. We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of studies using footnotes and will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Paediatric population up to 18 years and an adult population aged 18 years or over
2. Dosage of PDE-5 inhibitor
3. Mode of administration

We will use the following outcomes in subgroup analyses.

1. NYHA functional class
2. Mortality
3. Six-minute walk distance
4. Haemodynamic criteria

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

Sensitivity analysis

We plan to carry out the following sensitivity analyses.

- Exclusion of trials identified as at high risk of selection bias
- Fixed-effect model compared with random-effects model

ACKNOWLEDGEMENTS

This protocol was developed with the assistance of the Cochrane Airways protocol template, and comments were provided by the Cochrane Airways Group. The search strategy was developed with

assistance from Liz Stovold, the Cochrane Airways Group's Information Specialist. We thank the Cochrane Airways editors for their comments, including Rebecca Normansell. We acknowledge the authors Parthipan Kanthapilai and E. Haydn Walters for their previously published review.

Christopher Cates was the Editor for this review and commented critically on the review.

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 (NIHR), via Cochrane Infrastructure funding to Cochrane Airways. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS), or the Department of Health.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy to identify relevant studies from the Cochrane Airways Group Register of Trials

Proposed MEDLINE search strategy

1. exp Hypertension, Pulmonary/
2. Pulmonary Heart Disease/
3. (pulmonary adj2 hypertensi$).tw.
4. 1 or 2 or 3
5. exp Phosphodiesterase 5 Inhibitors/
6. (PDE5 or PDE-5).tw.
7. ("Phosphodiesterase 5" or Phosphodiesterase-5).tw.
8. (sildenafil or viagra).tw.
9. (tadalafil or Cialis).tw.
10. (vardenafil or Levitra or Staxyn).tw.
11. (avanafil or Stendra).tw.
12. or/5-11
13. 4 and 12
14. (controlled clinical trial or randomized controlled trial).pt.
15. (randomized or randomised).ab,ti.
16. placebo.ab,ti.
17. dt.fs.
18. randomly.ab,ti.
19. trial.ab,ti.
20. groups.ab,ti.
21. or/14-20
22. Animals/
23. Humans/
24. 22 not (22 and 23)
25. 21 not 24
26. 13 and 25

CONTRIBUTIONS OF AUTHORS

HB and ZB drafted the protocol, and AB and TW provided comments and changes.

DECLARATIONS OF INTEREST

HB: none known

ZB: none known

AB: none known

TW: Actelion Australia Scientific Advisory Board and Research/Education unrestricted grant; GSK Australia Scientific Advisory Board; Bayer Australia Scientific Advisory Board

SOURCES OF SUPPORT

Internal sources

- The authors declare that no such funding was received for this systematic review, Other.

External sources

- The authors declare that no such funding was received for this systematic review, Other.