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Ambulatory oxygen for people with chronic obstructive pulmonary disease who are not hypoxaemic at rest.

Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD000238.

DOI: [10.1002/14651858.CD000238.pub2](https://doi.org/10.1002/14651858.CD000238.pub2).

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Ambulatory oxygen for people with chronic obstructive pulmonary disease who are not hypoxaemic at rest (Review)

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[Intervention Review]

Ambulatory oxygen for people with chronic obstructive pulmonary disease who are not hypoxaemic at rest

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ABSTRACT

Background

People with chronic obstructive pulmonary disease (COPD) often become transiently hypoxaemic (low oxygen levels in blood) on exercise, necessitating oxygen therapy to improve breathlessness and exercise capacity and to reduce disability. Ambulatory oxygen therapy refers to provision of oxygen therapy during exercise and activities of daily living. Ambulatory oxygen therapy is often used by patients on long-term oxygen therapy (LTOT) during exercise or by non-LTOT users with or without resting hypoxaemia when they show evidence of exercise de-saturation and demonstrate improvement in exercise capacity with supplemental oxygen.

Objectives

To determine the longer-term efficacy of ambulatory oxygen therapy only in patients with COPD who do not meet the criteria for LTOT, with respect to improvement in exercise capacity, mortality, quality of life and other relevant measures of improvement.

Search methods

The Cochrane Airways Group Specialised Register, including MEDLINE, EMBASE and CINAHL, was searched. Online clinical trial registers, including Controlled Clinical Trials (www.controlled-trials.com), government registries (clinicaltrials.gov) and World Health Organization (WHO) registries (www.who.int/trialsearch), were screened for ongoing and recently completed studies. Bibliographies of included studies were searched for additional trials that may meet the inclusion criteria and were not retrieved by the above search strategy. Authors of identified trials were contacted to provide other published and unpublished studies. Searches were current as of November 2012.

Selection criteria

Randomised controlled trials (RCTs) that compare ambulatory oxygen therapy provided through portable oxygen cylinders/battery-powered devices or liquid oxygen canisters versus placebo air cylinders, usual medical care or co-intervention in study participants with COPD who did not meet criteria for LTOT.

Data collection and analysis

We used standard methods as expected by The Cochrane Collaboration.

Main results

Four studies met the inclusion criteria (331 participants), with two studies producing a statistically and clinically significant benefit in favour of the intervention for dyspnoea post exercise. The quality of life domain for all four included studies produced a statistically significant benefit for the subcategories of dyspnoea and fatigue, in favour of the oxygen group (dyspnoea mean difference (MD) 0.28, 95% confidence

interval (CI) 0.10 to 0.45; P value 0.002; fatigue MD 0.17, 95% CI 0.04 to 0.31; P value 0.009). No evidence of any effect was reported for survival, and limited benefits were observed for exercise capacity (as measured by step test and distance walk test), with one study showing a statistically significant improvement in the number of steps taken in the oxygen group for group N-of-1 studies only. No other statistically significant benefits were observed for exercise capacity among the other trials or individual N-of-1 studies.

Authors' conclusions

In patients with COPD with moderate hypoxia, current evidence on ambulatory oxygen therapy reveals improvements in dyspnoea post exercise and in the dyspnoea and fatigue domain of quality of life. However, evidence for the clinical utility and effectiveness of ambulatory oxygen in improving mortality and exercise capacity was not evident in this review. Methodologically rigorous RCTs with sufficient power to detect a difference are required to investigate the role of ambulatory oxygen in the management of COPD.

PLAIN LANGUAGE SUMMARY

Portable oxygen for chronic obstructive pulmonary disease

Background

Some people with chronic obstructive pulmonary disease (COPD) have low oxygen levels in their blood when they are resting or when moving. Low oxygen levels are known as hypoxaemia. These patients can carry around an oxygen supply (oxygen in small cylinders, portable liquid oxygen systems or battery-powered oxygen concentrators) so that they have oxygen to breathe to make simple tasks such as getting dressed, leaving the house, doing chores or even walking around their own home easier, and to help them to breathe. This portable oxygen device is referred to as 'ambulatory oxygen.'

Review question

We conducted this review to find out the long-term benefit of ambulatory oxygen therapy for people who are not severely hypoxaemic at rest.

Study characteristics

We looked at randomised controlled trials that compared ambulatory oxygen versus a placebo (normal air). We found four studies on 331 people with a mean age of 71 years. Two of the included studies were from Australia, one from New Zealand and one from Canada. The method of oxygen delivery and the dose of oxygen varied, although equipment in all instances consisted of light-weight or portable cylinders with flow ranging from 3 L/min to 6 L/min. Final follow-up was reported as 12 weeks for three studies and two weeks for the Nonoyama study.

Key results

We found that ambulatory oxygen therapy reduced breathlessness and decreased the number of patients who felt tired. However, the distance that people could walk in five to six minutes and survival (death rate) did not change.

Quality of the evidence

The overall quality of evidence from the studies in this review was moderate. The way the studies were conducted (methods) was not fully reported in all cases. Most studies were lacking the pre-published study plan (protocol).

Bottom line

From this review, it is not possible to know whether ambulatory oxygen therapy should be provided during exercise or for day-to-day activities for patients with COPD who are not severely hypoxaemic at rest.

This Cochrane plain language summary is up-to-date as of November 2012.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Ambulatory oxygen for COPD

Ambulatory oxygen for COPD

Patient or population: adults with COPD who had exertional dyspnoea but did not fulfil the criteria for long-term oxygen treatment

Settings: home and hospital

Intervention: ambulatory oxygen

Control: placebo/medical air

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Ambulatory oxygen				
Exercise capacity (5- or 6-minute walking distance on cylinder air) Follow-up: 2 to 12 weeks	See comment	See comment	Not estimable	331 (4 studies)	Not applicable	Meta-analysis not possible; see effects of interventions for more information
Mortality Follow-up: mean 12 weeks	See comment	See comment	RR 4.17 (0.48 to 36.3)	179 (2 studies)	⊕⊕⊕⊖ ¹ Moderate	Although deaths occurred only in the intervention arm of the study (n = 3), they were not believed to be a direct result of the intervention
Quality of life (dyspnoea) Measured on the CRQ, the output is a number from 0 to 7, where higher on the scale is better. MID is 0.5. Follow-up: 2 to 12 weeks	Baseline risk in control groups ranged from 2.8 to 3.7 points	Mean quality of life (dyspnoea) in the intervention groups was 0.28 higher (0.10 to 0.45 higher)	MD 0.28 (0.10 to 0.45)	341 (4 studies)	⊕⊕⊕⊖ ² Moderate	Other CRQ domains were also reported, including fatigue MD 0.14 (95% CI 0.04 to 0.31; P value 0.009), emotional function MD 0.10 (95% CI -0.05 to 0.25; P value 0.20) and mastery MD 0.13 (95% CI -0.06 to 0.33; P value 0.17)
Dyspnoea Follow-up: 6 to 12 weeks	See comment	See comment	Not estimable	198 (3 studies)	Not applicable	Meta-analysis not possible Dyspnoea was measured in 3 studies using the Borg scale, and 1 study reported dyspnoea during exercise. One study observed improvement in dyspnoea after walking for 6 minutes with cylinder air or oxygen. Another study showed a clinically rele-

						vant reduction in dyspnoea scores for the oxygen group post 5MWD compared with placebo
Adverse events Follow-up: mean 12 weeks	146 per 1000	117 per 1000 (35 to 325)	OR 0.77 (0.21 to 2.81)	83 (2 studies)	⊕⊕⊕⊕ low ^{1,3}	Only 1 of the adverse events appeared related to the intervention; this was strain due to carrying the cylinder
Hospitalisations	See comment	See comment	Not estimable	0 (0)	See comment	No studies reported data on hospitalisations

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

5MWD: 5-Minute Walking Distance test; **CI:** Confidence interval; **COPD:** Chronic obstructive pulmonary disease; **CRQ:** Chronic Respiratory Disease Questionnaire; **MD:** Mean difference; **MID:** Minimally important difference; **OR:** Odds ratio; **RR:** Risk ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Imprecision

² Unclear risk for selection bias in 2 studies, attrition bias in 2 studies and selective reporting in 3 studies

³ Unclear risk of selection bias, attrition bias and selective reporting in 1 study

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) primarily consists of chronic bronchitis and emphysema—conditions that are characterised by inflammation of the airways and destruction of pulmonary tissue. The diagnosis of COPD is based on documentation of a postbronchodilator forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) less than 70% of that predicted in an otherwise healthy person (Rabe 2007). COPD has variable illness trajectories characterised by worsening breathlessness, exercise limitations and progressive deterioration of quality of life (Seamark 2007). Exertional de-saturation (i.e. oxygen level in the blood decreases during exercise) and dyspnoea (breathlessness) are the markers of poor prognosis (Tham 2011). The mechanisms behind exertional hypoxaemia include ventilation/perfusion mismatch, shunting and limitations in diffusion capacity (Tham 2011). Many patients with COPD identify exertional dyspnoea as the key factor in functional decline (Nonoyama 2007). As the condition progresses, some patients become transiently hypoxaemic with exercise, necessitating oxygen therapy to attempt to improve breathlessness and exercise capacity, and to reduce disability (NICE 2010).

Description of the intervention

Ambulatory oxygen therapy refers to provision of oxygen during exercise, activities of daily living or both. It is often used during exercise by patients on long-term oxygen treatment (LTOT) or by non-LTOT users without resting hypoxaemia when they show evidence of oxygen de-saturation and demonstrate improvement in exercise capacity with supplemental oxygen (BTS 2006). Ambulatory oxygen therapy is usually provided in small oxygen cylinders lasting up to four hours at 2 L/min or through liquid oxygen systems that have a higher oxygen-carrying capacity lasting around six to 10 hours at 2 L/min (Bradley 2007). Ambulatory oxygen therapy can also be dispensed in an oxygen-conserving device (OCD) and with battery-powered portable oxygen concentrators. OCDs deliver bolus amounts of oxygen in response to the patient's inspiratory effort (or demand), as detected through a nasal cannula (Katsenos 2011). This system of oxygen delivery not only improves the duration of supply, it also improves the cost/benefit ratio of oxygen treatment. The battery-powered oxygen device weighs approximately 2 kg, which is about half the weight of an oxygen cylinder. The rationale of using these lightweight devices is that they improve compliance and facilitate ambulation; however, no known studies have validated this assumption to date.

How the intervention might work

Ambulatory oxygen has been shown to improve pulmonary hypertension and reduce dynamic hyperinflation in patients with COPD (Fujimoto 2002). Ambulatory oxygen may also delay diaphragmatic muscle fatigue and reduce lactic acidosis (Garrod 2000).

Why it is important to do this review

The prevalence of COPD is increasing worldwide, and COPD is associated with a variety of adverse effects for patients and the healthcare system. Dyspnoea, one of the most common symptoms of COPD, can be present at rest or during exercise, and this

can ultimately lead to reduced quality of life. Exercise training and supplemental oxygen (in advanced cases) are generally recommended for control of dyspnoea symptoms during exercise (ATS 1999). LTOT is usually prescribed for patients with severe hypoxia (i.e. partial pressure of oxygen in arterial blood (PaO₂) < 55 mmHg or PaO₂ of 55 to 59 mmHg with evidence of right heart failure). Current evidence suggests that LTOT improves survival and quality of life for these hypoxaemic patients with COPD (Ringbaek 2002; Stoller 2010). However, a significant proportion of patients with COPD do not have severe resting hypoxia but develop symptoms of severe hypoxia with exercise. Some studies suggest that in patients with stable COPD, 4% de-saturation during the six-minute walk test may predict long-term mortality (Casanova 2008). Unfortunately longer-term effects on survival time or quality of life of ambulatory oxygen in people with COPD with resting mild to moderate hypoxia and exertional dyspnoea or hypoxia remain unclear. Most relevant studies are inconclusive or have provided a short intervention period, used a small sample size or both (Jolly 2001; McDonald 1995). Hence it is important to perform a systematic review of trials of interventions to assess the current level of evidence for long-term ambulatory oxygen in this particular population.

OBJECTIVES

To determine the longer-term efficacy of ambulatory oxygen therapy only in patients with COPD who do not meet the criteria for LTOT, with respect to improvement in exercise capacity, mortality, quality of life and other relevant measures of improvement.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled parallel and cross-over trials.

Types of participants

Studies were included only when adult participants with stable COPD were randomly assigned. Participants had chronic hypoxaemia (resting PaO₂ 55 to 59 mmHg) without cor pulmonale (failure of the right side of the heart caused by an increase in blood pressure in the pulmonary artery, the vessel that carries blood from the heart to the lungs) or PaO₂ ≥ 60 mmHg, or they developed hypoxaemia on activity (PaO₂ < 60 mmHg or peripheral capillary oxygen de-saturation to < 88% SpO₂) with or without cor pulmonale with symptoms on exertion.

Types of interventions

The intervention was long-term ambulatory oxygen therapy (> two weeks) provided through portable oxygen cylinders or with the use of liquid oxygen canisters or battery-powered portable oxygen concentrators. Participants must have used ambulatory oxygen while at home. We included studies of greater than two weeks' duration.

Eligible control groups were given placebo air cylinders, usual medical care or other interventions (such as counselling).

Types of outcome measures

Primary outcomes

1. Exercise capacity on room air or on oxygen (e.g. timed walking tests, endurance tests).
2. Mortality.

Secondary outcomes

1. Dyspnoea scores (e.g. Borg scores, visual analogue scores).
2. Arterial oxygen saturation during exercise.
3. Recovery time after exercise.
4. Quality of life (measured using validated questionnaires such as St George's Respiratory Questionnaire (SGRQ) or the Chronic Respiratory Questionnaire (CRQ)).
5. Lung function measurements.
6. Adverse events.
7. Hospitalisation.
8. Length of stay.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and by handsearching of respiratory journals and meeting abstracts (see [Appendix 1](#) for further details). The search terms used in the previous version of the review were (portable* or ambulat*) and (oxygen*). For this version, the search terms were (portable* or ambulat* or mobil* or transport* or travel*) and (oxygen* or O2 or LTOT). The search was run on all records coded as 'COPD'.

In addition, we conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov), Controlled Clinical Trials (www.controlled-trials.com) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/).

We searched all databases from their inception to the present, with no restriction on language of publication. The latest searches were conducted in November 2012.

Searching other resources

We searched bibliographies of included studies for potentially relevant trials that were not retrieved by the above search strategy. We contacted authors of included studies to ask if they knew of other relevant published or unpublished studies. We searched online clinical trial registers, including Controlled Clinical Trials (www.controlled-trials.com), government registries (clinicaltrials.gov) and WHO registries (www.who.int/trialsearch), for ongoing and recently completed studies.

Data collection and analysis

Selection of studies

A combination of three review authors (FA, KC, ZU) independently assessed in duplicate the retrieved citations for inclusion, using titles, abstracts and/or descriptors. We then retrieved full-

text documents, and the same three review authors screened these for inclusion in duplicate. All trials identified as relevant but not meeting the inclusion criteria were re-discussed before final exclusion. Complete agreement was reached (after discussion) between all review authors working independently on classification of studies for inclusion and exclusion.

Data extraction and management

All study data were extracted by one of the three review authors and were verified by a second review author. Two review authors extracted risk of bias data independently (FA, KC, ZU). Conflicts were resolved by discussion with the third party.

Assessment of risk of bias in included studies

Two review authors (FA, KC, ZU) assessed each study for risk of bias for allocation sequence generation, allocation concealment, blinding of participants and outcome assessors, handling of missing data, selective outcome reporting and other threats to validity in the studies, in line with recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We conducted a retrospective risk of bias assessment using the above method applied to all original studies included in the review for the 2009 update.

Measures of treatment effect

We extracted and analysed continuous and dichotomous outcome data using standard statistical techniques with a fixed-effect model for all studies deemed similar enough to be pooled. In the presence of significant heterogeneity, we employed a random-effects model.

For continuous outcomes, we calculated mean differences (MDs) with 95% confidence intervals (CIs) and pooled values as MDs or standardised mean differences (SMDs). For dichotomous outcomes, we calculated risk ratios (RRs) with 95% CIs.

A narrative synthesis was performed for each of the included studies. All trials were combined using Review Manager software.

Unit of analysis issues

A mixture of cross-over and parallel studies were included in the review, with the potential for unit of analysis issues to occur. We used the generic inverse variance (GIV) method (by entering the effect estimates and their standard errors) to adjust for unit of analysis errors when meta-analysing the data, as per Section 7.7.7 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Dealing with missing data

We evaluated missing information regarding participants on an available case analysis basis, as described in Chapter 16.2.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). When statistics essential for analysis were missing (e.g. group means and standard deviations for both groups were not reported) and could not be calculated from other data, we attempted to contact the study authors to obtain the missing data. Loss of participants that occurred before baseline measurements were taken was assumed to have no effect on eventual outcome data provided by the study. Any losses that occurred after baseline measurements had been taken were assessed and discussed on an intention-to-treat basis.

Assessment of heterogeneity

Statistical heterogeneity was assessed using a combination of tests, including an I^2 statistic of 50% or greater and visual inspection of the data. If 10 or more studies had been included, we would also have used funnel plots. The Der-Simonian and Laird method of analysis presented with a P value less than 0.05 was considered statistically significant.

In the presence of significant heterogeneity (as per the criteria above), we reanalysed data using both fixed-effect and random-effects models.

Assessment of reporting biases

We planned to explore potential reporting biases by using a funnel plot if we were able to meta-analyse 10 or more studies. Instead we extrapolated on this possible risk of bias within the other bias section in the risk of bias tables.

Data synthesis

We analysed data from trials using RevMan 5.1.

Summary of findings tables

We assessed the quality of evidence as high, moderate, low or very low in accordance with recommendations outlined by the GRADE working group for meta-analyses of randomised trials ([GRADE website](#)). We have presented these assessments in a summary of findings table alongside the results of our analyses for the following

outcomes: exercise capacity (minute walking distance); mortality; quality of life.

Subgroup analysis and investigation of heterogeneity

If sufficient numbers of studies had been included, subgroup analyses would have been performed for:

1. oxygen therapy type (oxygen cylinder vs liquid oxygen therapy); and
2. duration of follow-up (short term ($\leq$ six months), medium term ($>$ six months to $\leq$ 12 months) and long term ($>$ 12 months)).

Sensitivity analysis

We planned to conduct a sensitivity analysis based on risk of bias. However, we did not conduct a sensitivity analysis, as none of the included studies were assessed to be at high risk of bias.

RESULTS

Description of studies

See [Characteristics of included studies](#) and [Characteristics of excluded studies](#).

Results of the search

From the 188 citations identified by the literature search, 26 full-text articles were considered relevant and were screened for eligibility ([Figure 1](#)). Four studies met all of the criteria for inclusion within the review, and seven studies were excluded although still considered relevant.

Figure 1. 158 Study flow diagram.

Included studies

Details of the four included studies are reported in the [Characteristics of included studies](#) table, and reasons for exclusion of seven studies are reported in the [Characteristics of excluded studies](#) table.

Study design

All four included studies investigated the efficacy of ambulatory oxygen for participants with COPD using a randomised cross-over design (McDonald 1995; Eaton 2002), a parallel randomised controlled design (Moore 2011) or an N-of-1 randomised controlled design (Nonoyama 2007) (the definition of an N-of-1 randomised controlled trial is one in which a single individual participant acts as the sole unit of observation in a study investigating the efficacy or side effect profiles of different interventions). Included studies were published between 1995 and 2011. Two studies originated from Australia (McDonald 1995; Moore 2011), one from Canada (Nonoyama 2007) and one from New Zealand (Eaton 2002).

Participant characteristics

A total of 331 participants were included across the four included studies, all of whom were adults with a mean age of 71 years. Sample sizes varied from 36 to 166. Mean PaO₂ ranged from 55 mmHg (Moore 2011) to 69 mmHg (Eaton 2002). Characteristics of participants in the McDonald 1995 study were PaO₂ > 60 mmHg

(> 8.0 kPa) and exertional dyspnoea limiting their daily activities. For the Eaton 2002 study, PaO₂ was 69 ± 7.5 mmHg (9.2 ± 1.0 kPa) with SpO₂ on exertion and room air 82 ± 5.4, whilst the Moore 2011 study participants had a PaO₂ > 55 mmHg (> 7.3 kPa) at rest on room air. Finally, participants in the Nonoyama 2007 study did not meet the criteria for long-term oxygen therapy and had exertional de-saturation of 88% or less; dyspnoea limited their daily activities. All participants across studies had variable degrees of oxygen saturation (refer to the [Characteristics of included studies](#) table for additional details).

Intervention characteristics

All included studies compared oxygen cylinders with an identical placebo of air or a composite of air and oxygen. Method of delivery and dose of oxygen varied, although the apparatus in all instances consisted of lightweight or portable cylinders, with flow ranging from 3 L/min to 6 L/min. Final follow-up was reported as 12 weeks for three studies (Eaton 2002; McDonald 1995; Moore 2011) and two weeks for the remaining study (Nonoyama 2007). The duration of intervention in McDonald and Eaton was six weeks, Moore 12 weeks and Nonoyama two weeks.

Outcomes

Outcome measures included mortality for two studies (McDonald 1995; Moore 2011), exercise capacity (as measured by step test

or walk distance test) in all four studies and dyspnoea measured by the Borg scale in participants at rest in one study (McDonald 1995) and after exercise in two others (Eaton 2002; Nonoyama 2007). Quality of life was reported in all four studies using the CRQ (Chronic Respiratory Questionnaire), arterial oxygen saturation during exercise was measured in two studies (McDonald 1995; Nonoyama 2007) and after exercise in one (Eaton 2002) and two studies described adverse events during the study period (Eaton 2002; McDonald 1995). None of the included studies reported data for hospitalisation, length of stay or recovery time post exercise.

Excluded studies

Seven studies appeared relevant from the initial screen but on further investigation did not meet all of the inclusion criteria. These were excluded from the analyses for the following reasons. Three studies (Bradley 2007; Fujimoto 2002; Jolly 2001) evaluated the

short-term effects of oxygen in single-assessment acute studies. Casaburi 2012 was a head-to-head study in which the comparison arm received an electronic portable oxygen concentrator, another study (Lacasse 2005) assessed the effects of ambulatory oxygen on participants who were already receiving LTOT and participants in another study (Lilker 1975) fulfilled the criteria for LTOT ($\text{PaO}_2 < 60$ mmHg with evidence of cor pulmonale). Another study (Gorecka 1997) evaluated the effect of LTOT in participants with COPD with moderate hypoxia.

Risk of bias in included studies

Full details of our risk of bias judgements can be found under the risk of bias section at the end of each [Characteristics of included studies](#) table. Key features highlighting potential risks of bias are summarised in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Eaton 2002	?	?	+	+	?	?	+
McDonald 1995	+	+	+	+	+	?	?
Moore 2011	+	+	+	+	+	+	+
Nonoyama 2007	?	?	+	+	?	?	+

Allocation

Allocation sequence generation

Two studies ([Moore 2011](#); [McDonald 1995](#)) reported an adequate method of sequence generation, and the remaining two studies ([Eaton 2002](#); [Nonoyama 2007](#)) were unclear. Adequate methods include the use of a computer-generated programme for randomisation.

Allocation concealment

Allocation concealment was adequately reported in two studies ([Moore 2011](#); [McDonald 1995](#)), in which allocation was undertaken by the supplier of the cylinder. The remaining two studies ([Eaton 2002](#); [Nonoyama 2007](#)) were unclear, as the methods of allocation concealment were not reported.

Blinding

Blinding of both participants and outcome assessors was adequately reported in all four studies.

Incomplete outcome data

Incomplete outcome data were adequately addressed in two studies ([Moore 2011](#); [McDonald 1995](#)), and the method was unclear in the remaining two studies ([Eaton 2002](#); [Nonoyama 2007](#)). The two studies assessed as unclear did not discuss the presence or absence of potential missing data within questionnaires for outcome collection.

Selective reporting

One study was free of selective outcome reporting ([Moore 2011](#)) with an online prespecified protocol, whilst the remaining three studies were unclear.

Other potential sources of bias

Other potential sources of bias were not identified in three studies ([Eaton 2002](#); [Moore 2011](#); [Nonoyama 2007](#)), whilst this could not be adequately assessed in the [McDonald 1995](#) study.

Effects of interventions

See: [Summary of findings for the main comparison Ambulatory oxygen for COPD](#)

See also [Summary of findings for the main comparison](#) for a summary of key comparisons.

Exercise capacity

Four studies on 267 randomly assigned participants (n = 331 when doubling up for cross-over and N-of-1 studies) reported exercise capacity through 'minute walking distance' via six-minute walking distance (6MWD) ([Eaton 2002](#); [McDonald 1995](#); [Moore 2011](#)) or five-minute walking distance (5MWD) ([Nonoyama 2007](#)). In the [Eaton](#) study, exercise capacity was assessed as an acute and short-term response and therefore could not be analysed in this review of 'long-term' treatment. The manuscript provides P values only for the impact of distance walked on oxygen, depending on long-term use of cylinder air or oxygen (P value 0.9); therefore we have not included in the meta-analysis the results of the 6MWD from the [Eaton 2002](#) study. From the remaining three studies, the 6MWD outcome was split into three categories, depending on whether

exercise capacity was assessed through 6MWD using cylinder air or oxygen or a cylinder similar to the one participants had used while they were at home. When exercise capacity was assessed through 6MWD using cylinder air ([McDonald 1995](#); [Moore 2011](#)) or cylinder oxygen ([McDonald 1995](#)), no statistically or clinically significant benefit was seen to favour the intervention group (cylinder air MD 1.19, 95% CI 0.80 to 1.77; P value 0.38; [Analysis 1.1](#); cylinder oxygen MD 1.27, 95% CI 0.48 to 3.39; P value 0.63; [Analysis 1.2](#)). Authors of the [Nonoyama 2007](#) study reported a statistically significant improvement in the number of steps taken by participants when on oxygen compared with placebo for group N-of-1 RCTs (MD 14.90, 95% CI 0.85 to 28.94; P value 0.04); however, no statistically significant effect was observed for individual N-of-1 RCTs. A step exercise test was also performed in the [McDonald 1995](#) study, and no difference was observed between groups ([Analysis 1.3](#)).

Mortality

Two studies on 179 participants (of whom 86 were on oxygen and 93 on air) reported deaths during the study periods. Two people in the intervention group of [McDonald 1995](#) died (cerebrovascular accident and overwhelming pneumonia), as did one participant in the intervention group of [Moore 2011](#). Although deaths occurred only in the intervention arms of these studies, they were not believed to be a result of the intervention. When data were pooled in a meta-analysis, the outcome favoured the control group; however this was not statistically significant (RR 4.17, 95% CI 0.48 to 36.32; [Analysis 1.4](#)).

Dyspnoea scores

Dyspnoea was measured in three studies using the Borg scale, with [McDonald 1995](#) (52 participants) reporting on dyspnoea during the 6MWD (MD -0.60, 95% CI -1.39 to 0.19) and during the step exercise test (MD -0.60, 95% CI -1.28 to 0.08; [Analysis 1.5](#)). A statistically significant improvement in acute post-6MWD dyspnoea scores was reported with cylinder oxygen by authors for the [Eaton 2002](#) study (cylinder oxygen 4.1 ± 1.8 ; cylinder air 4.8 ± 1.5 ; P value 0.005; 39 participants); however, over the six-week study period, no difference in dyspnoea that was dependent on whether participants were assigned to cylinder air or cylinder oxygen was observed on cylinder oxygen. The [Nonoyama 2007](#) study also produced a statistically significant reduction in dyspnoea scores for the oxygen group post 5MWD compared with placebo (MD -0.44, 95% CI -0.86 to -0.02; P value < 0.05; 27 participants).

Arterial oxygen saturation during exercise

One cross-over study with 26 participants ([McDonald 1995](#)) measured arterial oxygen saturation during exercise for the 6MWD (MD -0.60, 95% CI -2.32 to 1.12) and for the step exercise test (MD -0.60, 95% CI -2.32 to 1.12), neither of which produced a statistically or clinically significant difference between groups ([Analysis 1.6](#)).

Quality of life

Four studies on 331 participants reported quality of life using the CRQ ([Eaton 2002](#); [McDonald 1995](#); [Moore 2011](#); [Nonoyama 2007](#)). A statistically significant difference favoured the oxygen group for the pooled dyspnoea component (MD 0.28, 95% CI 0.10 to 0.45; P value 0.002) and the fatigue component (MD 0.17, 95% CI 0.01 to 0.32; P value 0.009). However, pooled results for emotional function

(MD 0.10, 95% CI -0.05 to 0.25) and mastery (MD 0.13, 95% CI -0.06 to 0.33) showed no evidence of an effect ([Analysis 1.7](#)).

Lung function measurements

Saturation of peripheral oxygen (SpO₂) on oxygen was measured in two studies on 136 participants, one during exercise ([Nonoyama 2007](#)) and the other after the 6MWD test ([Eaton 2002](#)); both produced a statistically and clinically significant difference in favour of the group that received ambulatory oxygen (MD 6.52, 95% CI 5.21 to 7.83; P value < 0.00001; [Analysis 1.8](#)). SpO₂ is an indirect measurement using a finger probe, ear sensor or similar device.

Adverse events

Adverse events were not among the prespecified outcomes in the included studies. However, two studies on 83 participants reported adverse events during the intervention period. [Eaton 2002](#) reported the development of co-morbidities (n = 2) and a cancer diagnosis (n = 1) in one participant during the control phase of the cross-over, and in another participant (n = 1) in the oxygen phase of the cross-over. [McDonald 1995](#) reported that three participants withdrew from the study during the first six weeks from the control group as the result of acute gout, muscular pain related to pulling the gas cylinder and unwillingness to continue further in the study; four participants withdrew during the second six weeks from the oxygen group as the result of two deaths (one from a cerebrovascular accident and another from overwhelming pneumonia), hospitalisation due to acute exacerbation of COPD and an incidental injury. No significant difference was observed when these events were pooled (odds ratio (OR) 0.77, 95% CI 0.21 to 2.81; [Analysis 1.9](#)). None of the included studies reported oxygen-related complications such as CO₂ retention and fire hazard.

Hospitalisation

No studies reported data for this outcome.

Length of stay

No studies reported data for this outcome.

DISCUSSION

Summary of main results

The primary aim of this review was to assess the effects of ambulatory oxygen in people with COPD who have exertional hypoxia or are not hypoxic at rest. All of the included studies reported as an outcome the primary outcome for this review, exercise capacity, leading to the overall sample size of 331 participants. All four studies reported this outcome as distance walked during the 6MWT or the 5MWT. Although the meta-analysis favoured the intervention group, benefit did not reach statistical or clinical significance. One study not included in the meta-analysis did produce statistically significant improvements in the oxygen group in the 5MWT for group N-of-1 studies; however, this effect was not observed for individual N-of-1 studies. Mortality, the other primary outcome in our review, was reported by only two studies ([McDonald 1995](#); [Moore 2011](#)). Overall, three deaths were reported in the intervention group; however, these events were not statistically significant, and the deaths were unlikely to be caused by the intervention. It is difficult to interpret mortality on the basis of results from cross-over studies and follow-up of short duration; therefore, these results are limited and should

be interpreted with caution. Two studies ([Eaton 2002](#); [Nonoyama 2007](#)) reported dyspnoea post exercise (6MWT or 5MWT), and both studies indicated statistically and clinically significant benefits in favour of oxygen. One study ([McDonald 1995](#)) reported dyspnoea and oxygen de-saturation during 6MWT and exercise testing; however, no significant change was noted. Quality of life was reported by all four included studies using the CRQ. Statistically significant improvement was observed for the dyspnoea and fatigue domains, although no significant improvements were noted for emotional function or mastery. Adverse events were reported by two studies ([Eaton 2002](#); [McDonald 1995](#)). None of the included studies reported incidents of oxygen-related fire or CO₂ retention. Although three participants in one control group reported muscular pain related to pulling cylinders, no significant difference was observed in the pooled analysis. Length of stay, rate of hospitalisation and spirometry were not reported in any of included studies.

Overall completeness and applicability of evidence

Despite an extensive literature search and the high burden of disease in the community, only four studies met our inclusion criteria. The primary aim of this review was to address the possible benefit of supplementary/ambulatory oxygen in mildly to moderately hypoxic patients for exercise capacity and mortality. Although only four studies met the inclusion criteria of this review, the overall sample size for the primary outcome of exercise capacity was moderate (n = 331). Other outcomes such as quality of life, dyspnoea and adverse events were not consistently reported amongst the included studies. We report a statistically significant mean difference of 0.28 (0.1 to 0.45) for the pooled dyspnoea component of the CRQ, favouring the oxygen group. However, this improvement needs to be interpreted in relation to the known minimally important difference (MID) of 0.5. This review provides a reasonable pooled analysis of relevant outcomes for the population with COPD requiring ambulatory oxygen; however, methodologically sound trials of sufficient power to allow confidence in the results are lacking. Good methodological rigour would include publication of a prespecified protocol outlining trial design, adequate sequence generation, randomisation, blinding (for participants and for outcome assessors) and transparent reporting of appropriate outcomes at baseline in a format suitable for meta-analysis (e.g. mean and corresponding standard deviation and sample size).

Quality of the evidence

The overall quality of included studies in this review was moderate. Methodology not always explicitly reported. Most included studies did report the methods used to blind assessors and participants from allocation; however, not enough information was provided for assessment of incomplete outcome data in two of four studies. Also, most studies did not have a prepublished protocol, which again increases the potential for selective outcome reporting. Sensitivity analysis was not conducted, as none of the included studies were assessed to be at high risk of bias.

Potential biases in the review process

No significant biases were anticipated or were found to occur during the review process. Criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* were strictly followed to limit the potential for bias during screening, data

extraction and analyses of included studies. Risk of bias was independently assessed by two review authors, and conflicts were resolved by discussion with a third review author. Corresponding authors of one included study (Nonoyama 2007) were contacted for raw data and clarification of methodological techniques. In response to Feedback 1, a second study author team were contacted for clarification of methodology (Moore 2011). No conflicts of interests, financial or otherwise, were reported for any of the review authors of this meta-analysis.

Agreements and disagreements with other studies or reviews

The utility of ambulatory oxygen in patients who do not fulfil the criteria for continuous long-term oxygen therapy is controversial. Similar to this review, the previous Cochrane review (Ram 2002) derived no firm conclusion from available evidence about the effectiveness of this intervention in patients with COPD and mild hypoxaemia. Our review does not fully support the prescription of ambulatory oxygen in patients with moderate hypoxaemia and exercise de-saturation, per guidelines of the British Thoracic Society (BTS 2006).

AUTHORS' CONCLUSIONS

Implications for practice

As a result of the limitations in methodological quality for some studies (due to lack of reporting) and lack of evidence to determine treatment effect on exercise capacity, mortality and quality of life, it is difficult to draw any firm conclusions about the use of ambulatory oxygen therapy in patients not meeting criteria for LTOT. However some statistical benefits were observed for dyspnoea post exercise and for the dyspnoea and fatigue domains of the Chronic Respiratory Questionnaire. Prescription of ambulatory oxygen therapy is recommended in current clinical practice guidelines for patients with moderate hypoxaemia ($\text{PaO}_2 > 7.3 \text{ kPa}$) who are not

on LTOT but do show exercise de-saturation (with a fall in SpO_2 of 4% to a value $< 90\%$), improvement in exercise capacity and/or less breathlessness with ambulatory oxygen therapy (BTS 2006). The discrepancy between current clinical practice and available evidence from this review has important clinical implications. First, patients may be prescribed ineffective treatment, which may result in functional limitations from pulling oxygen cylinders and cylinder tubing. Second, oxygen therapy is an expensive treatment for both patients and the healthcare system, with ongoing prescriptions of ambulatory oxygen producing significant financial burdens for both. The decision to prescribe ambulatory oxygen for patients not meeting the criteria for LTOT (in an attempt to improve dyspnoea) should be made on a case-by-case basis until sufficient evidence has been obtained to support the clinical application of ambulatory oxygen.

Implications for research

Few long-term studies of ambulatory oxygen have been conducted in participants with COPD. The role of ambulatory oxygen therapy in patients with COPD with moderate hypoxia requires further investigation through adequately powered RCTs of sufficient methodological quality (including a prespecified published protocol, adequate sequence generation, randomisation, blinding and outcome reporting); in particular, the outcomes listed in the results section of this meta-analysis should be assessed in all future studies.

ACKNOWLEDGEMENTS

We would like to thank all staff at the Cochrane Airways Group, in particular Emma Welsh, Elizabeth Stovold, Emma Jackson and Chris Cates for their ongoing help and support. We also wish to thank peer reviewers for their time and valuable feedback.

Michael Greenstone was the Editor for this review and commented critically on the review.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Eaton 2002

Methods	<p>Country: New Zealand</p> <p>Design: randomised double-blind cross-over study</p> <p>Study objective: to assess the short-term clinical impact of ambulatory oxygen in participants with severe COPD and significant exercise de-saturation who did not fulfil the criteria for LTOT, and to determine whether baseline characteristics or acute response predicts short-term response</p> <p>Methods of analysis: Treatment and order of treatment were included in the model with participant as random effect. Logistic regression was used to investigate factors that predict short-term response to cylinder oxygen</p> <p>Clustering adjustments made: not applicable</p>
Participants	<p>Eligible for study: n = 57</p> <p>Randomised: intervention n = 25, control n = 25</p> <p>Completed: n = 41 participants in total (cross-over)</p> <p>Age: 67.1 ± 9.3 years</p> <p>Gender: male 70%</p> <p>Hypoxemia diagnosis: resting PaO₂ 9.2 ± 1.0 kPa. SpO₂ on exertion and room air 82 ± 5.4; all participants needed to complete 6 weeks of rehabilitation and had to be clinically stable for longer than 2 months with standard optimal medical care</p> <p>Co-morbidities included: none reported</p> <p>Exclusion criteria: limiting angina or significant musculoskeletal disability</p>
Interventions	<p>Intervention description: prefilled pink-painted lightweight oxygen cylinder at flow rate of 4 L/min for any activity that would induce dyspnoea</p> <p>Control description: prefilled pink-painted lightweight air cylinder at flow rate of 4 L/min for any activity that would induce dyspnoea</p> <p>Duration of intervention: 6 weeks for each arm</p>

Eaton 2002 (Continued)

Setting: outpatient clinics and pulmonary rehabilitation referrals to Green Lane Hospital, Auckland, New Zealand; ambulatory participants

Outcomes *Prespecified outcomes:* 6-minute walking distance, SpO₂, Borg scale and health-related quality of life measures

Follow-up period: 12 weeks

Notes *Funding:* funded by the Health Research Council of New Zealand

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation mentioned; however methods not described
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All cylinders identical in appearance (painted pink) and prefilled, with unique cylinder numbers for researcher identification purposes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study authors report that assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participant attrition reported; however potential missing data within questionnaires and outcome collection not mentioned or accounted for in analyses
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit a judgement of yes or no
Other bias	Low risk	No other biases identified

McDonald 1995

Methods *Country:* Australia

Design: randomised double-blind cross-over study

Study objective: to assess the short-term effects of oxygen therapy on exercise capacity and the longer-term effects on both exercise capacity and quality of life of ambulatory oxygen used during ordinary activities at home in participants with severe COPD, without severe resting arterial hypoxaemia

Methods of analysis: paired t-tests for continuous variables; Wilcoxon test for discrete variables, with carry-over effects measured by 2-sample Mann-Whitney and t-tests

Clustering adjustments made: not applicable

Participants *Eligible for study:* not reported

Randomised: n = 36 participants in total (cross-over)

Completed: n = 26 participants in total (cross-over)

McDonald 1995 (Continued)

Age: 73 ± 6 years

Gender: male n = 24, female n = 2

Hypoxemia diagnosis: participant PaO₂ greater than 60 mmHg; exertional dyspnoea limited daily activities

Co-morbidities included: not reported

Exclusion criteria: symptomatic cardiac dysfunction, angina pectoris and locomotor disability

Interventions	<p><i>Intervention description:</i> oxygen in a portable gas cylinder (Stroller 682; Medical Gases) at flow rate of 4 L/min for any activity that would induce dyspnoea</p> <p><i>Control description:</i> air in a portable gas cylinder (Stroller 682; Medical Gases) at flow rate of 4 L/min for any activity that would induce dyspnoea</p> <p><i>Duration of intervention:</i> 6 weeks for each arm</p> <p><i>Setting:</i> outpatient domiciliary</p>
Outcomes	<p><i>Prespecified outcomes:</i> exercise capacity (step test and 6-minute walking distance), quality of life (CRQ), dyspnoea, SaO₂</p> <p>(SaO₂ is a direct measurement using a blood sample such as an arterial blood gas analysis).</p> <p><i>Follow-up period:</i> 12 weeks</p>
Notes	<p><i>Funding:</i> supported by the Sir Edward Dunlop Research Foundation and by Medical Gases, Australia</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors report the use of a computer-generated list of random odd or even numbers
Allocation concealment (selection bias)	Low risk	Study authors report concealed allocation, assignment undertaken by the gas cylinder company
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants are said to be blinded to the intervention/control through the use of identical apparatus
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study authors report that assessors performing the tests were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participant attrition reported with reasons
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit a judgement of yes or no
Other bias	Unclear risk	Insufficient information to permit a judgement of yes or no

Moore 2011

Methods	<p><i>Country:</i> Australia</p> <p><i>Design:</i> prospective parallel, double-blind, randomised controlled trial</p> <p><i>Study objective:</i> to perform a large, adequately powered study to determine the effects of domiciliary ambulatory oxygen in participants with COPD and exertional dyspnoea, without severe resting hypoxaemia, with or without exercise de-saturation. A further aim was to identify factors that might predict any observed benefit</p> <p><i>Methods of analysis:</i> transition dyspnoea index scores and cylinder utilisation data analysed using t-tests to compare treatment means; other outcome measures analysed using 2-way, repeated-measures analysis of variance; a priori variables selected to identify subgroup differences, which study authors believed may benefit differentially from domiciliary ambulatory oxygen; data analysed using ANCOVA, with week 12 values as the response variable, the corresponding value at baseline as the co-variate and each of the subgroup variables as an explanatory factor, in addition to treatment (air or oxygen)</p> <p><i>Clustering adjustments made:</i> not applicable</p>
Participants	<p><i>Eligible for study:</i> n = 1318 (assessed for eligibility); enrolled n = 160</p> <p><i>Randomised:</i> intervention n = 68, control n = 75</p> <p><i>Completed:</i> intervention n = 66, control n = 73</p> <p><i>Age:</i> intervention 72 ± 9.2, control 72 ± 10.4 years</p> <p><i>Gender:</i> females enrolled = 44; distribution across arms not reported</p> <p><i>Hypoxemia diagnosis:</i> PaO₂ > 7.3 kPa at rest breathing room air</p> <p><i>Co-morbidities included:</i> not reported</p> <p><i>Exclusion criteria:</i> current smoking, clinically unstable COPD, current participation in a pulmonary rehabilitation programme, current domiciliary oxygen use, significant communication or locomotor difficulties or other severe medical conditions</p>
Interventions	<p><i>Intervention description:</i> cylinder oxygen, weighing 4.2 kg filled, provided with a trolley/stroller with gas delivered at a flow rate of 6 L/min via the Impulse Elite conservation device (AirSep Corporation, Buffalo, New York, USA)</p> <p><i>Control description:</i> cylinder air of identical appearance to the intervention</p> <p><i>Duration of intervention:</i> no recommendations provided regarding duration of use; however end of study was at 12 weeks, following a 2-week run-in period</p> <p><i>Setting:</i> participants recruited through database screening and advertisements; cylinders used inside and outside the home during exertional activities</p>
Outcomes	<p><i>Prespecified outcomes:</i> dyspnoea, health-related quality of life, exercise tolerance, activity levels, depression symptoms, service utilisation, mood disturbance, functional status and gas utilisation</p> <p><i>Follow-up period:</i> following 2-week run-in period, 4-week (mid-trial) assessment and 12-week (end of study) assessment</p>
Notes	<p><i>Funding:</i> funded by National Health and Medical Research Council, Northern Clinical Research Centre, Victorian Tuberculosis and Lung Association, Austin Hospital Medical Research Foundation, Institute for Breathing and Sleep, Austin Hospital, Australia Finkel Foundation, Air Liquide, Boehringer Ingelheim</p>
Risk of bias	
Bias	Authors' judgement Support for judgement

Moore 2011 (Continued)

Random sequence generation (selection bias)	Low risk	Study authors report the use of a computer-generated programme for randomisation
Allocation concealment (selection bias)	Low risk	Study authors report concealed allocation, assignment undertaken by supplier of the portable cylinders
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Cylinders were of identical appearance, and study authors report that participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study authors report that study personnel were blinded to group allocation, as assignment was undertaken by supplier of the portable cylinders
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study authors report attrition with reasons, and 'complete data' for all participants
Selective reporting (reporting bias)	Low risk	Pre-specified protocol published; outcomes match those in the publication
Other bias	Low risk	No other biases identified

Nonoyama 2007

Methods	<p><i>Country:</i> Canada</p> <p><i>Design:</i> N-of-1 double-blind, randomised controlled trial (participants undertook 3 pairs of 2-week treatment periods)</p> <p><i>Study objective:</i> to measure the effects of oxygen in participants with COPD who do not meet criteria for mortality reduction with long-term oxygen therapy</p> <p><i>Methods of analysis:</i> Analysis of each N-of-1 RCT included a paired t-test; effect of oxygen on entire group was measured by analysis of variance; paired t-tests were used to measure within-group differences</p> <p><i>Clustering adjustments made:</i> not applicable</p>
Participants	<p><i>Eligible for study:</i> n = 178</p> <p><i>Randomised:</i> n = 38</p> <p><i>Completed:</i> n = 27</p> <p><i>Age:</i> 69 ± 10 years</p> <p><i>Gender:</i> male = 17, female = 10</p> <p><i>Hypoxemia diagnosis:</i> participants with COPD who do not meet the criteria for long-term oxygen therapy for mortality reduction, with symptoms of dyspnoea limiting daily activities and with de-saturation of 88% or less for 2 continuous minutes during a room air 6MWD</p> <p><i>Co-morbidities included:</i> not reported</p> <p><i>Exclusion criteria:</i> participants with COPD who meet the criteria for long-term oxygen therapy for mortality reduction (i.e. PaO₂ < 55 mmHg at rest or PaO₂ of 55 to 60 at rest with right heart failure); partic-</p>

Nonoyama 2007 (Continued)

ipants already on oxygen for palliative care or nocturnal hypoxaemia; inability to provide consent or complete questionnaires

Interventions	<p><i>Intervention description:</i> oxygen at 1 to 3 L/min. Participants completed walking oximetry while breathing room air, followed by titration of oxygen to establish the flow rate necessary to maintain saturation at 92% or greater during each of the N-of-1 RCTs</p> <p><i>Control description:</i> placebo mixture of air and oxygen (24%) at 2 L/min that provided a fraction of inspired oxygen (FiO₂) of approximately 21.2%</p> <p><i>Duration of intervention:</i> 3 pairs of 2-week treatment periods</p> <p><i>Setting:</i> West Park Healthcare Centre; testing occurred in the participant's home</p>
Outcomes	<p><i>Prespecified outcomes:</i> quality of life (CRQ—dyspnoea, fatigue, mastery and emotional status domains, and SGRQ—dyspnoea as measured by modified Borg scale); exercise capacity as measured by 5MWD</p> <p><i>Follow-up period:</i> 3 pairs of 2-week treatment periods</p>
Notes	<i>Funding:</i> supported by the Ontario Ministry of Health and Long Term Care

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation mentioned; however methods not described
Allocation concealment (selection bias)	Unclear risk	Study authors report that allocation was concealed; however methods not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants are said to be blinded to the intervention/control through the use of identical apparatus
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study authors report that assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participant attrition reported; however potential missing data within questionnaires and outcome collection not mentioned or accounted for in analyses
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit a judgement of yes or no
Other bias	Low risk	No other biases identified

5MWD: 5-Minute Walking Distance test; ANCOVA: Analysis of co-variance; COPD: Chronic obstructive pulmonary disease; CRQ: Chronic Respiratory Questionnaire; LTOT: Long-term oxygen therapy; PaO₂: Partial pressure of oxygen in arterial blood; RCTs: Randomised controlled trials; SaO₂: arterial oxygen saturation; SpO₂: Peripheral capillary oxygen saturation.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bradley 2007	Short-term/acute study; not a study of long-term ambulatory oxygen therapy
Casaburi 2012	Control group E-cylinders (electronic portable cylinders); not placebo, air or co-intervention
Fujimoto 2002	Short-term/acute study; not a study of long-term ambulatory oxygen therapy
Gorecka 1997	Evaluation of the effects of long-term oxygen therapy (LTOT) in participants with COPD with moderate hypoxia
Jolly 2001	Short-term/acute study; not a study of long-term ambulatory oxygen therapy
Lacasse 2005	Assessment of outcomes in participants who were already receiving long-term oxygen therapy
Lilker 1975	Participants already fulfilling criteria for LTOT ($\text{PaO}_2 < 60$ mmHg with evidence of cor pulmonale)

COPD: Chronic obstructive pulmonary disease; LTOT: Long-term oxygen therapy; PaO_2 : Partial pressure of oxygen in arterial blood.

DATA AND ANALYSES

Comparison 1. Ambulatory oxygen therapy versus placebo (air)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 6MWD (cylinder air for 6MWD)	2		Odds Ratio (Fixed, 95% CI)	1.05 [0.62, 1.75]
2 6MWD outcome (cylinder oxygen for 6MWD)	1		Odds Ratio (Fixed, 95% CI)	Totals not selected
3 Step exercise testing (number of steps)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Mortality	2	179	Risk Ratio (M-H, Fixed, 95% CI)	4.17 [0.48, 36.32]
5 Borg score—dyspnoea (higher score worse)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 During 6MWD	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 During step exercise test	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Arterial oxygen saturation during exercise	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 During 6MWD	1	52	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.56, 0.36]
6.2 During step exercise test	1	52	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.32, 1.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Quality of life (Chronic Respiratory Questionnaire)	4		Mean Difference (Fixed, 95% CI)	Subtotals only
7.1 CRQ—dyspnoea	4		Mean Difference (Fixed, 95% CI)	0.28 [0.10, 0.45]
7.2 CRQ—fatigue	4		Mean Difference (Fixed, 95% CI)	0.17 [0.04, 0.31]
7.3 CRQ—emotional function	4		Mean Difference (Fixed, 95% CI)	0.10 [-0.05, 0.25]
7.4 CRQ—mastery	4		Mean Difference (Fixed, 95% CI)	0.13 [-0.06, 0.33]
8 SpO₂	2	136	Mean Difference (IV, Fixed, 95% CI)	6.52 [5.21, 7.83]
8.1 During exercise	1	54	Mean Difference (IV, Fixed, 95% CI)	6.0 [4.11, 7.89]
8.2 Post 6MWD	1	82	Mean Difference (IV, Fixed, 95% CI)	7.0 [5.18, 8.82]
9 Adverse event	2	83	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.21, 2.81]

Analysis 1.1. Comparison 1 Ambulatory oxygen therapy versus placebo (air), Outcome 1 6MWD (cylinder air for 6MWD).

Analysis 1.2. Comparison 1 Ambulatory oxygen therapy versus placebo (air), Outcome 2 6MWD outcome (cylinder oxygen for 6MWD).

Analysis 1.3. Comparison 1 Ambulatory oxygen therapy versus placebo (air), Outcome 3 Step exercise testing (number of steps).

Study or subgroup	Oxygen Group		Air Group		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
McDonald 1995	26	33 (18)	26	30 (17)		3[-6.52,12.52]
					Favours air	Favours oxygen

Analysis 1.4. Comparison 1 Ambulatory oxygen therapy versus placebo (air), Outcome 4 Mortality.

Study or subgroup	Oxygen Group		Air Group		Risk Ratio	Weight	Risk Ratio
	n/N	n/N	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
McDonald 1995	2/18	0/18	0/18	0/18		51.24%	5[0.26,97.37]
Moore 2011	1/68	0/75	0/75	0/75		48.76%	3.3[0.14,79.77]
Total (95% CI)	86	93	93	93		100%	4.17[0.48,36.32]
Total events: 3 (Oxygen Group), 0 (Air Group)							
Heterogeneity: Tau ² =0; Chi ² =0.03, df=1(P=0.85); I ² =0%							
Test for overall effect: Z=1.29(P=0.2)							
					Favours oxygen		Favours air

Analysis 1.5. Comparison 1 Ambulatory oxygen therapy versus placebo (air), Outcome 5 Borg score—dyspnoea (higher score worse).

Study or subgroup	Oxygen Group		Air Group		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.5.1 During 6MWD						
McDonald 1995	26	3.2 (1.4)	26	3.8 (1.5)		-0.6[-1.39,0.19]
1.5.2 During step exercise test						
McDonald 1995	26	3.7 (1.1)	26	4.3 (1.4)		-0.6[-1.28,0.08]
					Favours oxygen	Favours air

Analysis 1.6. Comparison 1 Ambulatory oxygen therapy versus placebo (air), Outcome 6 Arterial oxygen saturation during exercise.

Study or subgroup	Oxygen Group		Air Group		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
1.6.1 During 6MWD							
McDonald 1995	26	3.2 (2)	26	3.8 (1.5)		100%	-0.6[-1.56,0.36]
Subtotal ***	26		26			100%	-0.6[-1.56,0.36]
Heterogeneity: Not applicable							
Test for overall effect: Z=1.22(P=0.22)							
1.6.2 During step exercise test							
					Favours oxygen		Favours air

Analysis 1.7. Comparison 1 Ambulatory oxygen therapy versus placebo (air), Outcome 7 Quality of life (Chronic Respiratory Questionnaire).

Analysis 1.8. Comparison 1 Ambulatory oxygen therapy versus placebo (air), Outcome 8 SpO₂.

Analysis 1.9. Comparison 1 Ambulatory oxygen therapy versus placebo (air), Outcome 9 Adverse event.

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
CENTRAL (<i>The Cochrane Library</i>)	Monthly
MEDLINE (Ovid)	Weekly

(Continued)

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

Handsearches: core respiratory conference abstracts

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

MEDLINE search strategy used to identify trials for the CAGR

COPD search

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

Filter to identify RCTs

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

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

FEEDBACK**Feedback, 17 July 2014****Summary**

We note with interest the updated Cochrane review on “Ambulatory oxygen for chronic obstructive pulmonary disease”. We are concerned that the review has some major limitations that require addressing. We have detailed our concerns below but broadly they go to the clinical validity of the questions posed in the review, the assessment of trial quality and the evidence synthesis itself.

Outcome measure selection. Why was mortality included and in particular why as a primary outcome? Ambulatory oxygen is clinically an adjuvant therapy provide with the aim of alleviating hypoxaemia and dyspnoea during activity. What is the evidence that ambulatory oxygen for these clinical indications and typically delivered at low to moderate flow rates, would be expected to modify mortality?

Dyspnoea data reporting including the summary of findings table. The aims of the review clearly state that dyspnoea is included as a secondary outcome yet the data from Moore et al 2011 are not included in the meta-analyses. While it is absolutely true that scores on the Borg scale and measures made on the BDI/TDI are not directly comparable as they tap into different domains and constructs, to fail to analyse the BDI data without an explanation is puzzling. Perhaps the authors could comment on this omission. The mean increase in CRQ Dyspnoea domain score is 0.28 (0.1 to 0.45). While the MID is quoted correctly at 0.5 there is no discussion in the review of the clinical significance of this result—that while there is a small positive benefit of oxygen on this measure the estimate and the associated confidence intervals are well within the MID. This omission speaks to the limited clinical utility of the review we believe.

Quality of the evidence. The assertion that the quality of the evidence in the included studies was low overall seems at odds with both the risk of bias tables and the narrative description of the studies. In the risk of bias table, the “failures” appeared predominantly to be failures of reporting rather than clear omissions and in the narrative it is noted that the “+” were all associated with low risk of bias. Why were the study authors not contacted to resolve these issues? In the largest included trial (Moore 2011) the narrative in the review notes that all quality domains were met and at n=143 randomised was larger than the other 3 studies combined (n=124)! It is this apparent disconnect between the narrative of the review and the summary/conclusions that is striking.

Thank you for your consideration and we look forward to your response. Regards.

Reply

Outcome measure selection. Mortality is an important outcome in many trials of COPD treatment. Pulmonary hypertension is one of the inevitable outcomes of COPD and ambulatory oxygen has been shown to improve pulmonary hypertension and reduce dynamic hyperinflation in patients with COPD (Fujimoto 2002). The relief of hypoxic pulmonary vasoconstriction with oxygen may contribute to a decrease in pulmonary hypertension and some studies suggest that in patients with stable COPD, 4% de-saturation during the six-minute walk test may predict long-term mortality (Casanova 2008). Unfortunately longer-term effects on survival time or quality of life of ambulatory oxygen in people with COPD with resting mild to moderate hypoxia and exertional dyspnoea or hypoxia remain unclear.

This led us to include mortality as well as exercise capacity as a primary outcome. However, the studies we identified for inclusion were of maximum 12 weeks' duration, leaving us unable to comment on the long term effects of ambulatory oxygen on mortality. Long-term mortality is important and unknown and we recognise that short term mortality is not a good surrogate. Therefore, we conclude that the decision to prescribe ambulatory oxygen should be made on a case-by-case basis until sufficient evidence has been obtained to support the clinical application of ambulatory oxygen.

Dyspnoea data reporting including the summary of findings table. We did not feel it was appropriate to meta-analyse data from the Moore study together with the other studies as they use the Borg score. However dyspnoea (measured by CRDQ) for the Moore study has indeed already been included in [Analysis 1.7](#). We have added information on the MID for dyspnoea to the discussion.

Quality of the evidence. In response to the feedback received, we have made the appropriate changes to the reporting on the risk of bias after receiving additional core data from study authors.

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WHAT'S NEW

Date	Event	Description
7 January 2015	Amended	<p>The review has been amended in response to feedback published with the review in July 2014. We requested and received information from the group who submitted the feedback about the conduct of the McDonald 1995 study and updated the risk of bias table. To view the full feedback comment and see Feedback 1.</p> <p>We also changed the judgements in the summary of findings table.</p>

HISTORY

Protocol first published: Issue 2, 1996

Review first published: Issue 3, 2001

Date	Event	Description
29 August 2014	Feedback has been incorporated	Feedback has been added to the review. The author team will incorporate the feedback in due course.
29 August 2014	Amended	Feedback received.
1 November 2012	New citation required and conclusions have changed	New studies added, text updated, risk of bias and summary of findings tables added. New review author team

Date	Event	Description
1 November 2012	New search has been performed	New literature search run
30 June 2008	Amended	Converted to new review format.
27 November 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Faisal Ameer is the lead investigator for this review. Contributions included completion and submission of the 'review update registration form' including development of the updated protocol for the review, screening and selection of studies for inclusion, data extraction, data entry, interpretation of the analysis and complete write-up of the manuscript draft.

Kristin Carson assisted with the 'review update registration form,' screening and selection of studies, data extraction, data entry, interpretation of analysis and write-up of the final manuscript.

Zafar Usmani screened and selected studies for inclusion, performed data extraction and data entry and assisted with interpretation of the analysis and write-up of the final manuscript.

Brian Smith supervised the review update process, interpreted the analysis and assisted with write-up of the final manuscript.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Respiratory Medicine Unit; The Queen Elizabeth Hospital, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There have been several amendments between the protocol and review for this update, including:

- Alteration to the objective of the review
- Definition of 'long term' given as >two weeks
- Types of participants revised as per the inclusion criteria
- Mortality included as primary outcomes instead of secondary outcome
- Length of stay, quality of life, adverse events and hospitalisations added as secondary outcomes
- Search terms truncated
- Cochrane risk of bias tool applied replacing the Jadad score
- Statistical methodology defined with greater detail
- Added summary of findings table

INDEX TERMS

Medical Subject Headings (MeSH)

Ambulatory Care; Exercise [physiology]; Hypoxia [therapy]; Oxygen Inhalation Therapy [*methods]; Pulmonary Disease, Chronic Obstructive [blood] [physiopathology] [*therapy]; Randomized Controlled Trials as Topic; Rest

MeSH check words

Humans