



Oxygen for relief of dyspnoea in people with chronic obstructive pulmonary disease who would not qualify for home oxygen: a systematic review and meta-analysis

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ABSTRACT

We searched MEDLINE, EMBASE and the Cochrane Controlled Trials Register to determine whether oxygen relieves dyspnoea in mildly or non-hypoxic COPD and included 18 randomised controlled trials (431 participants) in the meta-analysis using Cochrane methodology. Oxygen therapy reduced dyspnoea when compared with medical air; standardised mean difference -0.37 (95% CI -0.50 to -0.24 ; $I^2=14\%$). In a priori subgroup and sensitivity analyses, dyspnoea was reduced by continuous oxygen during exertion but not short-burst oxygen therapy. Continuous exertional oxygen can relieve dyspnoea in mildly or non-hypoxic COPD, but evidence from larger clinical trials is needed.

INTRODUCTION

Dyspnoea is a common and distressing symptom for patients with COPD. The management of dyspnoea includes optimised COPD treatment with bronchodilators, pulmonary rehabilitation, regular use of low-dose opioids and home oxygen therapy.

It is unknown whether oxygen relieves dyspnoea in patients with mild or non-hypoxic COPD (palliative oxygen). Home oxygen therapy does improve survival in COPD with severe hypoxaemia ($P_aO_2 \leq 7.3$ kPa) or mild hypoxaemia ($P_aO_2 7.4$ – 7.9 kPa) in the setting of pulmonary hypertension, cor pulmonale and/or secondary polycythaemia (haematocrit $>55\%$).¹ Effects of oxygen on symptoms, including dyspnoea, in mild to moderate hypoxaemia are unknown.

Despite sparse supporting evidence, palliative oxygen is frequently prescribed to improve dyspnoea. Oxygen therapy is, however, costly and may be ineffective or might cause complications including nasal irritation, burns secondary to smoking, hyperoxia-related vasoconstriction and exacerbation of hypercapnia. Data on the efficacy of palliative oxygen therapy are needed.

We therefore conducted a systematic review and meta-analysis to determine whether oxygen therapy provides symptomatic relief in COPD patients with breathlessness who do not qualify currently for long-term oxygen.

METHODS AND MATERIALS

This paper summarises the full 2011 review published by the Cochrane Library.²

Search strategy

We searched MEDLINE (1966 to November 2009), EMBASE (1980 to November 2009) and the Cochrane Airways Group Specialised Register (through November 2009) as detailed in the online supplement. Additional manuscripts were identified by searching references lists of articles and published reviews that met the inclusion criteria.

Study selection

Inclusion criteria were: (1) randomised controlled trial; (2) participants were adults with COPD; (3) mean $PaO_2 \geq 7.3$ kPa; (4) subjects were not already receiving home oxygen therapy; (5) oxygen versus medical air as intervention; (6) intervention delivered through non-invasive method (nasal cannula, mouthpiece or mask); and (7) dyspnoea as one study outcome. Two investigators (HEU, APA) screened abstracts independently. Differences in judgment were resolved by consensus conference. The flow of articles reviewed is presented in the online supplementary figure S1.

Data extraction

Basic study parameters were abstracted (by HEU and verified by APA) into evidence tables. When necessary, the authors of the primary studies were contacted to obtain additional information.

Types of oxygen therapy

The oxygen therapy was categorised as either short-burst when given for a short period pre-exertion or postexertion, or as continuous (during exertion and/or at rest) including domiciliary oxygen therapy.

Quality assessment

Each study was assessed for internal validity (randomisation, blinding and description of withdrawals/dropouts) and external validity (descriptions of subjects and interventions, and adequately reported dyspnoea outcomes) using the Jadad score (5-point scale; higher score indicating better validity), shown in online supplementary table S1.

Data analysis

The primary outcome of interest was the effect on patient-rated dyspnoea. Secondary outcomes were effect on quality of life (QOL) and patient treatment preference. Crossover comparisons were analysed,



when available, using paired tests. Correlations and SEs were calculated as described elsewhere.² Effect estimates measured on different dyspnoea scales were standardised by dividing each mean difference with its SD, giving the standardised mean differences (SMDs). Effect sizes were calculated for random-effects models using RevMan 5 (Cochrane Informatics and Knowledge Management, Oxford, UK) and reported as SMD with 95% CIs. Heterogeneity was described as the I^2 for each measure and explored through the following prespecified subgroup and sensitivity analyses: studies with mean $P_{aO_2} < 9.3$ compared with ≥ 9.3 kPa; studies of short-burst oxygen compared with other studies; and excluding studies using imputed data.

RESULTS

Excluded studies

Ten studies were not included in the meta-analysis due to insufficient data (seven crossover trials), significant order effect (one crossover trial) and lack of crossover comparisons (two parallel group studies). Five of the excluded studies reported that oxygen improved dyspnoea while four reported no significant effect.

Study characteristics

In total, 28 studies, comprising 31 study comparisons and 702 participants met the inclusion criteria (see online supplementary table S1). Of the 28 included studies, 23 were blinded, randomised, crossover trials and five were randomised, controlled, parallel arm trials.

Most studies required patients to have moderate to severe COPD for study entry. All studies compared oxygen with medical air; 23 studies (82%) provided continuous oxygen during exertion, four studies (14%) provided short-burst oxygen and one study provided oxygen at rest.

Study details are reported in online supplementary table S1. Methods were poorly reported in most of the included studies. While all studies were described as randomised, we could verify that sequence generation was adequate in only six studies. Masking of treatment was undertaken in a number of studies, but we were unable to determine how blinding had been achieved in five studies.

Treatment efficacy

Primary outcome: dyspnoea

This analysis included 18 studies (427 patients; 21 study comparisons) (figure 1). Oxygen relieved dyspnoea in mildly- or non-hypoxic COPD patients (SMD -0.37 , 95% CI -0.50 to -0.24) more effectively than medical air. Significant heterogeneity was not observed ($I^2=14\%$, $p=0.24$).

A priori subgroup and sensitivity analyses

Oxygen relieved dyspnoea both in studies with a mean $P_{aO_2} \geq 9.3$ kPa (12 studies; SMD -0.42 , 95% CI -0.61 to -0.24 ; $I^2=28\%$) and in studies with a mean $P_{aO_2} < 9.3$ kPa (six studies; SMD -0.25 , 95% CI -0.50 to -0.00 ; $I^2=14.2\%$), as shown in online supplementary figure S2.

The four studies of short-burst oxygen showed that the method did not relieve dyspnoea (SMD 0.01 , 95% CI -0.26 to 0.28 ; $I^2=0\%$), whereas 14 studies of continuous oxygen during exertion improved dyspnoea (SMD -0.46 , 95% CI -0.59 to -0.33 ; $I^2=0.0\%$) (see online supplementary figure S3).

Sensitivity analysis, using six studies for which SMD and variance, was obtained without any data imputation and showed a stable beneficial effect of oxygen on dyspnoea (SMD -0.36 , 95% CI -0.64 to -0.09 ; $I^2=59\%$).

Secondary outcomes: QOL and patient preference

Meta-analyses of secondary outcomes could not be performed due to heterogeneity in data presentation and outcome measurements.

QOL was reported in three of 28 included studies. One study found no statistically significant differences in the Chronic Respiratory Questionnaire (CRQ), Short Form 36 (SF-36), or the Hospital Anxiety and Depression Scale (HADS). The second study reported statistically significant improvements in all domains of the CRQ (fatigue, $p=0.02$; emotional function, $p=0.006$; mastery, $p=0.008$; total, $p=0.002$), both domains of the HADS (anxiety, $p=0.009$; depression, $p=0.05$) and in several domains of the SF-36. The third study found no statistically significant difference in the CRQ.

Blinded participant preferences were reported in three studies. In the first study, 41% of participants thought to be benefiting from oxygen did not wish to continue to receive

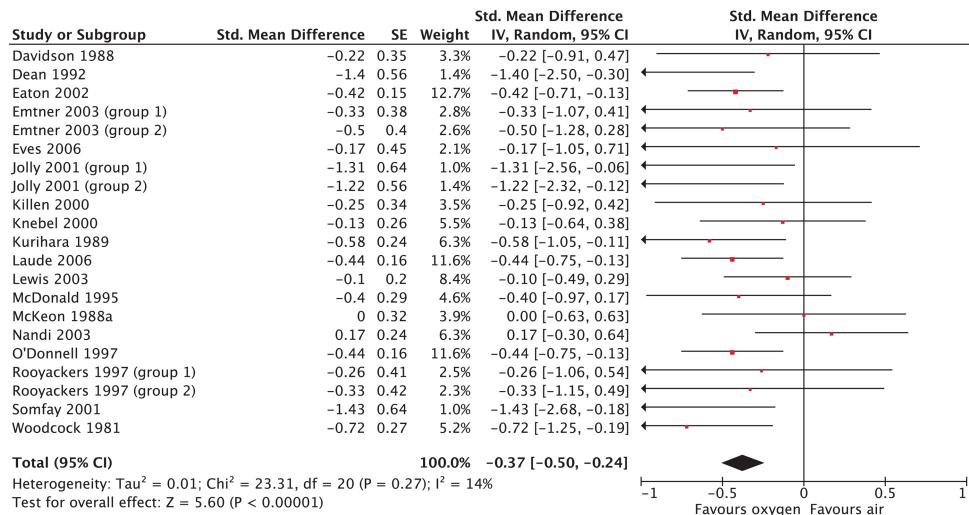


Figure 1 Forest plot summarising randomised trials of the symptomatic effect of oxygen on breathlessness in people with COPD who do not qualify for long-term oxygen therapy; all trials.

therapy, 76% citing poor tolerability as the reason. In the second study, 12 of 18 subjects preferred oxygen, five before going up the stairs and seven after completing the ascent. Of the remaining six patients, three preferred room air before going up the stairs and three had no preference. In the third study, after 6 weeks home therapy with each gas, half of the patients preferred oxygen while the other half either preferred air or had no preference.

DISCUSSION

Continuous oxygen during exertion, but not short-burst therapy, reduced dyspnoea in mildly- and non-hypoxic people with COPD who would not otherwise qualify for home oxygen therapy. The effect, SMD -0.46 (95% CI -0.59 to -0.33) translates into a clinically meaningful reduction of about 1.2 cm on a 10 cm VAS.³

Data on QOL and patient preference were sparse and conflicting making it impossible to perform a meta-analysis. The conflicting results may be due to differences or interactions of study design, patient population and small sample sizes. The burden imposed by home oxygen therapy may also outweigh any potential impact on QOL. Interestingly, 41% of 'oxygen responders' in one study did not desire further therapy owing mainly to inconvenience or poor tolerability. QOL and other patient factors should be considered when deciding whether the benefits of palliative oxygen outweigh its inconveniences. Further research is needed.

Several limitations are noteworthy. Baseline dyspnoea, functional status or both were not presented in many studies, making it difficult to assess whether the participants were similar.

In conclusion, continuous oxygen during exertion relieved dyspnoea in people with COPD who would not otherwise qualify for home oxygen therapy due to mild or absent hypoxaemia. The effect might be mediated by reduced exertional hypoxaemia. The observed heterogeneity of study designs, however, makes it difficult to provide general recommendations. Two double-blind, randomised trials published after the completion of the review reported no relief of breathlessness from palliative

oxygen when compared with medical air⁴ and no benefit from ambulatory oxygen.⁵ Decisions regarding prescription of oxygen for relief of dyspnoea in individuals not meeting criteria for long-term oxygen therapy should be made on an individual basis after careful consideration. Data from adequately powered clinical trials, including studies on cost-effectiveness, risk of possible hyperoxia-related adverse effects and fires, and future meta-analyses are needed to answer this question.

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Contributors HEU, DCC, DCM, GPS and APA performed the study design and analysis. HEU, MPE, DCC, DCM, GPS and APA participated in the interpretation of the findings, writing and revision of the paper.

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Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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- 2 Uronis H, McCrory DC, Samsa G, et al. Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011;(6): CD006429.
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Search strategies for Palliative oxygen in non-hypoxaemic COPD

THE COCHRANE SPECIALISED AIRWAYS REGISTER

(dyspnea OR dyspnoea OR breathlessness) AND (oxygen OR oxygen inhalation therapy OR O2 or LTOT) AND COPD (all as textword or index terms)

MEDLINE (1966 to present)

(Combined with RCT filter)

- 1 Dyspnea.mp
- 2 dyspnoea.mp
- 3 breathlessness.mp
- 4 or/1-3 (25112)
- 5 (oxygen\$ or O2).mp
- 6 exp OXYGEN INHALATION THERAPY/
- 7 (oxygen adj3 therap\$).mp
- 8 (long term oxygen therap\$ or LTOT).mp
- 9 respiratory therapy/
- 10 or/5-9
- 11 lung diseases, obstructive/ or bronchitis/ or exp bronchitis, chronic/
- 12 exp Pulmonary Disease, Chronic Obstructive/
- 13 (obstruct\$ adj3 (lung\$ or respirat\$ or pulmonar\$) adj3 disease\$).mp
- 16 (COPD or COAD).mp
- 17 or/11-16
- 18 4 and 10 and 17
- 19 exp "clinical trial [publication type]" /
- 20 (randomized or randomised).ab,ti.
- 21 placebo.ab,ti.
- 22 dt.fs.
- 23 randomly.ab,ti.
- 24 trial.ab,ti.
- 25 groups.ab,ti.
- 26 or/19-25
- 27 Animals/
- 28 Humans/
- 29 27 not (27 and 28)
- 30 26 not 29
- 31 18 and 30

EMBASE (1980 to present)

(Combined with RCT filter

- 1 exp dyspnea/ or Dyspnea.mp. or dyspnoea.mp. or breathlessness.mp.
- 2 (oxygen\$ or O2).mp.
- 3 exp OXYGEN INHALATION THERAPY/
- 4 (oxygen adj3 therap\$).mp.
- 5 (long term oxygen therap\$ or LTOT).mp.
- 6 respiratory therapy/
- 7 or/2-6
- 8 lung diseases, obstructive/ or bronchitis/ or exp bronchitis, chronic/
- 9 exp Pulmonary Disease, Chronic Obstructive/
- 10 (obstruct\$ adj3 (lung\$ or respirat\$ or pulmonar\$) adj3 disease\$).mp.
- 11 (Bronchiti\$ or emphysema\$).mp.
- 12 ((chronic adj5 obstruct\$) and (pulmonar\$ or lung\$ or airway\$ or airflow\$ or bronch\$ or respirat\$)).mp.
- 13 (COPD or COAD).mp.
- 14 Chronic Obstructive Lung Disease/
- 15 or/8-14
- 16 1 and 7 and 15
- 17 Randomized Controlled Trial/
- 18 Controlled Study/
- 19 randomization/
- 20 Double Blind Procedure/
- 21 Single Blind Procedure/
- 22 Clinical Trial/
- 23 Crossover Procedure/
- 24 follow up/
- 25 exp prospective study/
- 26 or/17-25
- 27 (clinica\$ adj3 trial\$).mp.
- 28 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (mask\$ or blind\$ or method\$)).mp.
- 29 exp Placebo/
- 30 placebo\$.mp.
- 31 random\$.mp.
- 32 (latin adj3 square\$).mp.
- 33 exp Comparative Study/
- 34 ((control\$ or prospectiv\$ or volunteer\$) adj3 (trial\$ or method\$ or stud\$)).mp.
- 35 (crossover\$ or cross-over\$).mp.
- 36 or/27-35
- 37 26 or 36

38 exp ANIMAL/
39 Nonhuman/
40 Human/
41 38 or 39
42 41 not 40
43 37 not 42
44 16 and 43

Supplementary figures

Figure S1. Article flow diagram

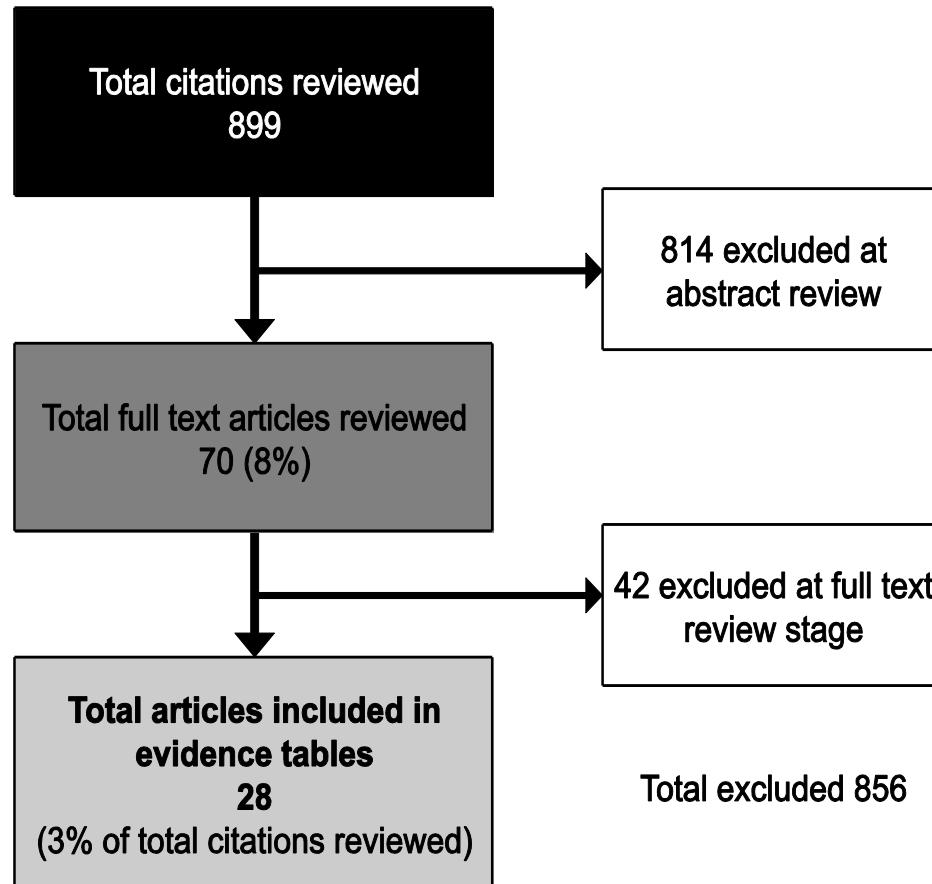


Figure S2. Forest plot summarizing randomised trials of the symptomatic effect of oxygen on breathlessness in people with chronic obstructive pulmonary disease (COPD) who do not qualify for long-term oxygen therapy (LTOT) dichotomised by baseline mean partial pressure of oxygen.

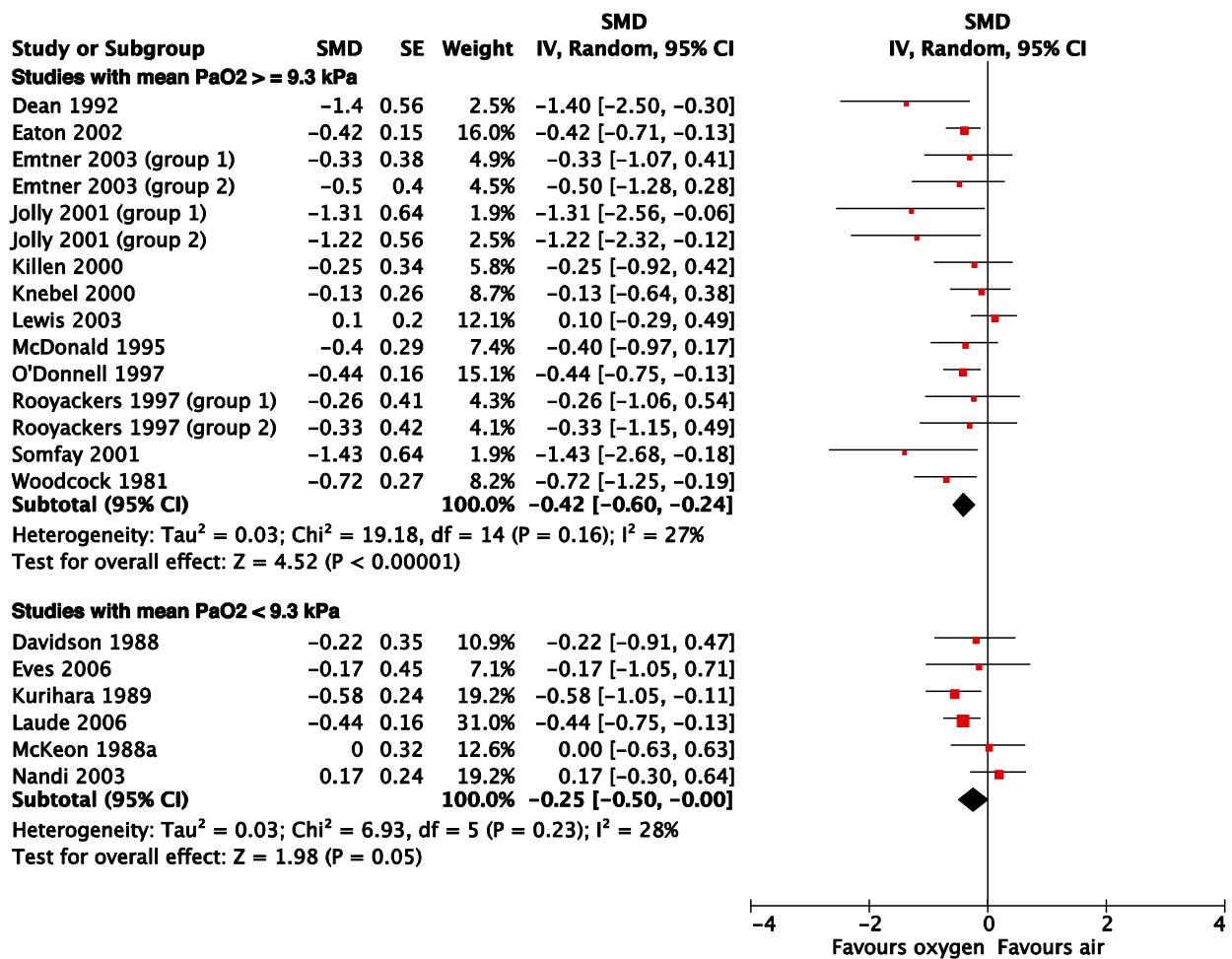
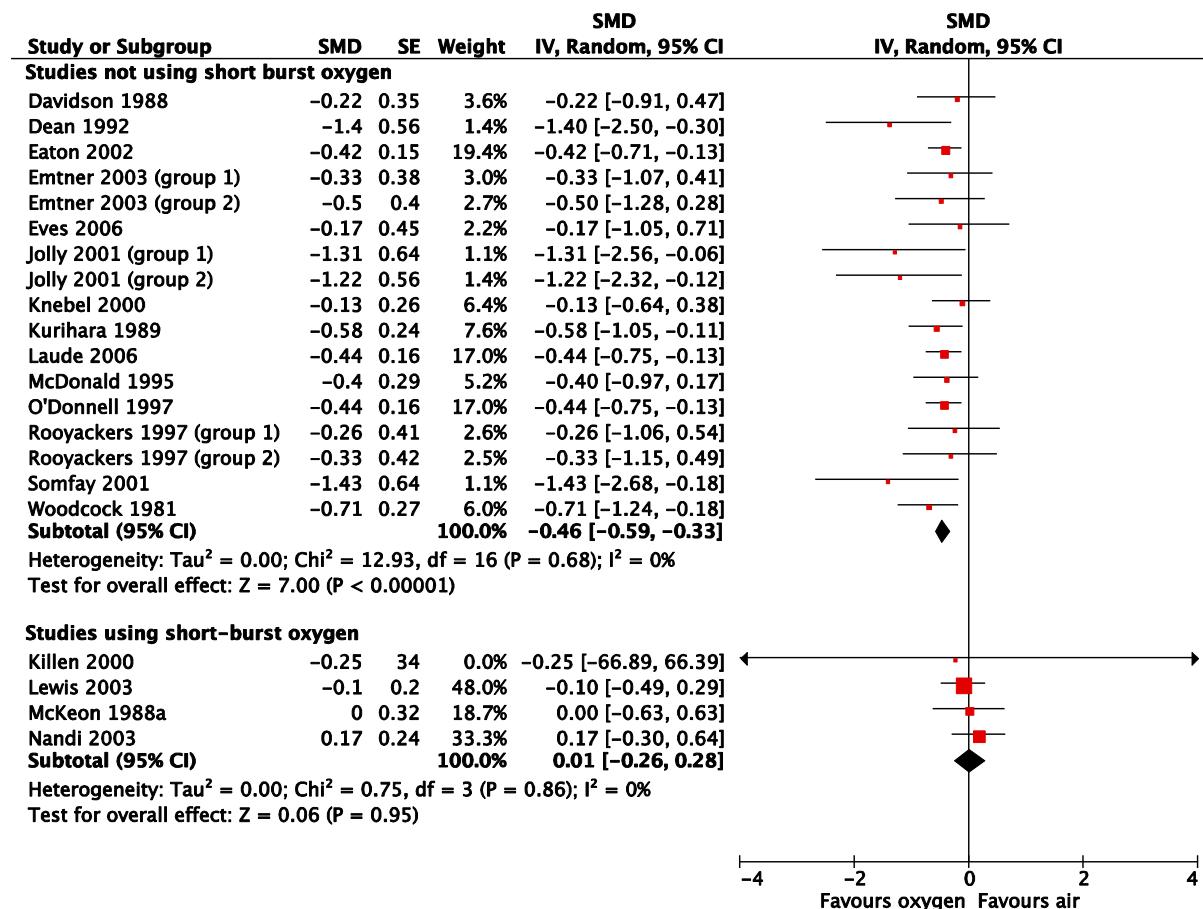


Figure S3. Forest plot summarizing randomised trials of the symptomatic effect of oxygen on breathlessness in people with chronic obstructive pulmonary disease (COPD) who do not qualify for long-term oxygen therapy (LTOT) dichotomised by duration of oxygen administered.



Online supplement

Oxygen for relief of refractory dyspnoea in people with chronic obstructive pulmonary disease who would not qualify for home oxygen: a systematic review and meta-analysis

Table S1. Clinical summary of included studies

Study	Design	Blinding	Baseline PaO ₂ (kPa)	Baseline SaO ₂ (%)	Dyspnoea measure	Baseline dyspnoea	O ₂ delivery	O ₂ dose	Exertion method	Jadad score
Moore 2009	Crossover	Double-blind	NA	94.6 (SD 3.2)	modified Borg	NA	Mouthpiece	44%	At rest	3
Eaton 2006	Parallel group	Double-blind	10.0	NA	CRQ	17.1	NC	2L/min	Domiciliary	4
Eves 2006	Crossover	Double-blind	9.1 (SD 0.9)	NA	modified Borg	NA	Mouthpiece	40%	Constant load cycle test	4
Laude 2006	Crossover	Unclear	NA	93.9 (2.3)	100mm VAS modified Borg	VAS 24.2 (19.0) Borg 1.8 (1.1)	Mask/valve	28%	Treadmill	1
Haidl 2004	Parallel group	Unblinded	8.9	NA	modified Borg	NA	NC	2L/min	Cycle ergometry	1
Emtner 2003 - Gp 1	Parallel group	Double-blind	9.8 (SD 0.8)	NA	modified Borg	NA	Mouthpiece	30%	Cycle ergometry	5
Emtner 2003 Gp 2	Parallel group	Double-blind	10.0 (SD 1.2)	NA	modified Borg	NA	Mouthpiece	30%	Cycle ergometry	5
Lewis 2003	Crossover	Single-blind	NA	94.4 (1.6)	modified Borg	0.4 (0.5)	NC	2L/min	6MWT	2
Nandi 2003	Crossover	Double-blind	NA	91.9 (5.2) (range 76 to 97)	100mm VAS	NA	Mask	4L/min	6MWT	3
Eaton 2002	Crossover	Double-blind	9.2 (SD 1.0)	NA	modified Borg	0.7 (SD 1.0)	NC	4L/min	6MWT	4
Jolly 2001 Gp 1	Crossover	Double-blind	10.5 (SE 0.4)	95.8 (0.46)	modified Borg	0.56 (SE 0.34)	NC	3L/min	6MWT	3
Jolly 2001 Gp 2	Crossover	Double-blind	9.9 (SE 0.3)	94.7 (SE 0.27)	modified Borg	1.27 (SE 0.43)	NC	3L/min	6MWT	2
Maltais 2001	Crossover	Double-blind	11.3 (SD 0.5)	NA	modified Borg	NA	Mouthpiece	75%	Incremental cycle test	2

Wadell 2001	Parallel group	Single-blind	Median 9.3 (range 7.9-11.4)	Median 94.6 (range 90.7-97.2)	modified Borg	Median 1.5 (range 0-3)	NC	5L/min	6MWT on treadmill	3
Somfay 2001	Crossover	Single-blind	NA	95.7 (0.8)	modified Borg	NA	Mouthpiece	30%	Constant load cycle test	1
Killen 2000	Crossover	Single-blind	NA	Median 94 (Quartiles 91, 95)	100mm VAS	NA	Mask	2L/min	Ascending 22 steps	3
Knebel 2000	Crossover	Double-blind	NA	97.1 (SD 1.7) (range 92-100)	100mm VAS	0.5 (SD 0.9) (range 0-4.7)	NC	4L/min	6MWT	5
Garrod 1999	Crossover	Single-blind	8.4 (SD 1.2)	NA	modified Borg	NA	NC	2L/min	Shuttle walk test	2
O'Donnell 1997	Crossover	Double-blind	9.9 (SEM 0.4)	NA	modified Borg	5.1 (SD 0.3)*	Mouthpiece	60%	Endurance cycle test	3
Rooyackers 1997 Gp 1	Parallel group	Unclear	10.2 (SD 1.2)	NA	modified Borg	NA	NC	4L/min	Cycle tests and 6MWT	1
Rooyackers 1997 Gp 2	Parallel group	Unclear	9.5 (2.0)	NA	modified Borg	NA	NC	4L/min	Cycle tests and 6MWT	1
Ishimine 1995	Crossover	Single-blind	10.1 (SD 1.1)	NA	Dyspnoea questionnaire	NA	Unknown	3L/min	6MWT	2
McDonald 1995	Crossover	Double-blind	9.2 (SD 1.1) (range 7.7-10.9)	94 (SD 2.1)	modified Borg	NA	NC	4L/min		4
Dean 1992	Crossover	Double-blind	9.5 (SE 0.3)	NA	modified Borg	NA	Mouthpiece	40%	Cycle ergometry	4
Leach 1992	Crossover	Single-blind	8.7 (SD 2.3)	NA	100mm VAS	NA	Mask	2L/min		3
Kurihara 1989	Crossover	Single-blind	9.2 (SD 1.2)	NA	modified Borg	NA	NC	3L/min		1
Davidson 1988	Crossover	Double-blind	8.6 (SE 0.3)	NA	100mm VAS	NA	NC or valve	4L/min	6MWT, cycle ergometry, and endurance walk	2
McKeon 1988a	Crossover	Double-blind	7.7 (SD 1.2) (range 5.7-10.9)	90 (SD 3) (range 84-96)	300mm VAS	NA	NC	2.5L/min	Incremental treadmill test	2
McKeon 1988b	Crossover	Double-blind	8.9 (SD 1.5)	NA	300mm VAS	NA	NC	4L/min	Incremental treadmill	5

									test	
Swinburn 1984	Crossover	Single-blind	NA	93.2 (SD 0.8)	100mm VAS	NA	Mouthpiece	60%	Incremental cycle test	1
Woodcock 1981	Crossover	Double-blind	9.6 (SD 1.5)	NA	100mm VAS	4 (SD 0.94)**	NC	4L/min	Treadmill and 6MWT	3

Key: 6MWT = six minute walk test, NA = not available, VAS = visual analog scale, CRQ = chronic respiratory questionnaire, SD = standard deviation, SE = standard error, NC = nasal canula

Data presented as mean (standard deviation (SD)) unless otherwise specified. The Jadad score assesses internal validity (randomisation, blinding, and description of withdrawals/dropouts) and external validity (descriptions of subjects and interventions, and adequately reported dyspnoea outcomes) on a five point scale with higher scores indicating better validity.

* As measured by dyspnoea index

** As measured by MRC dyspnoea grade

Studies in shaded rows were not included in meta-analyses.