Bijlage Evidencetabellen

VRAAG 1: Medicamenteuze behandeling dyspneu in palliatieve fase

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Ben-Aharon I 2012	• SR + MA • Funding/CoI: authors declare no CoI • Search date: November 2011 • Databases: PubMed, CENTRAL, EMBASE, conference proceedings • Study designs: RCTs • N included studies: 12 relevant (out of 18)	• Eligibility criteria: Terminal Cancer patients experiencing dyspnoea • Patient characteristics: ○ Age 20-90 years	Intervention for dyspnoea relief (opioids n=226, benzodiazepines n=164, furosemide, n=22) compared with any alternative / placebo	Dyspnoea: VAS-score dyspnoea relief Opioids vs Placebo: 3 Studies/ 69 patients; -1.31; 95%CI -2.49 to -0.13 Benzodiazepines vs morphine vs combination of both: 2 studies, but no combination of results (Navigante 2006, Navigante 2010) Exercise tolerance: Not reported Physical functioning: Not reported Quality of life: Not reported	• SR of moderate quality: broad search, duplicate selection; not clear which quality criteria exactly were used • Included RCTs: Mazocatto1999, Bruera 1993, Davis 1996, Grimbert 2004, Charles 2008, Clemens 2009, Bruera 2005, Allard 1999, Navigante 2006, Navigante 2010, Wilcock 2008, Stone 2002
Jennings AL 2001	• SR + MA • Funding/CoI: Supported by Royal Marsden Hospital and Systematic Review Training Unit, London/CoI none known; • Search date: May 1999 • Databases: Medline, Embase, CINAHL, Cochrane Library, etc • Study designs: RCTs • N included studies: N=18	• Eligibility criteria: Patients of any age with advanced disease suffering from breathlessness	Intervention of any opioid drug against placebo for relief of breathlessness	Dyspnoea: Breathlessness: Based on 12 studies (196 patients). SMD = -0.31; 95%CI -0.50 to -0.13, p=0.0008 Exercise tolerance: Based on 12 studies (115 patients) SMD = 0.20; 95%CI -0.03 to 0.42, p=0.09 Physical functioning: Not reported Quality of life: Not reported	• SR of high quality • Included RCTs: Beauford 1993, Bruera 1993, Chua 1997, Davis 1994, Davis 1996,Eiser 1991a, Eiser 199b, Harris-Eze1995, Jankelson 1997, Johnson 1983, Leung 1996, Light 1996, Masood 1995, Noseda 1997, Poole 1998, Woodcock 1981, Woodcock 1982, Young 1989

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Marciniuk DD 2011	• SR / Guideline • Funding/CoI: No external funding source/ online-declaration of CoI • Search date: Jan 1996 - March 2009 • Databases: Medline, Embase, Cochrane Library, Canadian Medical Association InfoBase, National Guideline Clearinghouse. • Study designs: Different study types • N included studies: N=13	• Eligibility criteria: Patients with advanced chronic obstructive pulmonary disease (COPD) experiencing dyspnoea	1. Treatment using anxiolytic and antidepressant medication (including benzodiazepines considered here, 4studies with 52 patients) 2. Treatment using opioids (7 separate studies with 197 patients)	Narrative presentation of results	• SR of moderate quality: no search strategy provided, unclear how quality appraisal was done • Included RCTs: Mitchell-Heggs 1980, Woodcock 1981, Man 1986, Green 1989 (case report); Eiser 1991, Poole 1998, Johnson 1983, Woodcock 1981, Woodcock 1982, Abernethy 2003, Currow 2009, Jennings 2002, Brown 2005
Simon ST 2013	• SR • Funding/CoI: German Federal Ministry of Education and research grant; three researchers are responsible for clinical trial on the buccal administration form of fentalyl funded by TEVA Ltd. • Search date:1950 - June 2012 • Databases:Medline, Embase, Cochrane Library, International Pharmaceutical Abstracts • Study designs: RCTs, case studies, before-after studies • N included studies: N=13	• Eligibility criteria: patients of any disease suffering from breathlessness	Intervention using fentanyl (or dugs belonging to the same pharmacological group) to treat breathlessness	Dyspnoea: Breathlessness (episodic and continuous) considered, no combination of data from different studies; only narrative: all studies described improvement regarding the sensation of breathlessness Exercise tolerance: Not reported Physical functioning: Not reported Quality of life: Not reported	• SR of moderate quality: broad search, quality appraisal results not reported • Included RCTs: Benitez Rosario 2005, Burburan 2009, Coyne 2002, Gauna 2008, Gika 2010, Graff 2004, Jensen 2012, Mercadante 1999, O'Siorain 1998, Sitte 2009, Sitte 2008, Smith 2009, Trujillo Vilchez 2005

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Simon ST 2010	• SR • Funding/CoI: King's College London, UK and Werner Jackstaedt Foundation, Germany; declared no CoI • Search date: September 2009 • Databases: 14 data bases including Cochrane Pain, Palliative and Supportive Care Trials, CENTRAL, CDSR, DARE, MEDLINE, EMBASE, CINAHL,etc • Study designs: RCTs, CCTs • N included studies: N=7	• Eligibility criteria: Patients with advanced stages of cancer, chronic obstructive pulmonary disease, chronic heart failure, motor neurone disease and idiopathic pulmonary fibrosis. Excluded were cases with acute or chronic asthma, pneumonia or other curable diseases	Use of benzodiazepines for the relief of breathlessness compared to placebo or active control N=200 patients	<u>Dyspnoea</u>: Overall: Placebo-controlled (4 studies/128 pts) SMD: -0.13; 95%CI -0.52 to 0.25 Morphine-controlled (2 studies/107 pts) SMD: -0.68; 95%CI -2.21 to 0.84 Breathlessness - no relief: placebo /controlled (2 stds/50pts): RR 0.88 ; 95%CI 0.56-1.39 morphine /controlled (1 stds/55pts): RR 1.74 ; 95%CI 0.91-3.32 Breathlessness – breakthrough: After 48hours (2 stds/108 pts): RR 0.76 ; 95%CI 0.53-1.09 After 24hours (2 stds/116 pts): RR 0.97 ; 95%CI 0.71-1.34 <u>Exercise tolerance</u>: narrative description only 12 minutes walking: no difference found in 2 studies, significant impairment reported in 1 study <u>Physical functioning</u>: Not reported <u>Quality of life</u>: Not reported	• SR of high quality • Included RCTs: Eimer 1985, Harrison (unpublished), Man 1986, Navigante 2006, Navigante (unpublished), Shivaram 1989, Woodcock 1981
Bailey 2010	• SR of SRs • Funding/CoI: The Breathlessness Research Charitable Trust, UK and National Cancer Research Institute; authors have no competing interests • Search date: July 2007- September 2009 • Databases: Cochrane Library, AMED, CINAHL, EMBASE, Ovid MEDLINE, PsycINFO • Study designs: SRs • N included studies:	• Eligibility criteria: adult patients with breathlessness within a wide range of non-malignant, cardiorespiratory disease	Opioids Corticosteroids	Narrative reporting of results	• SR of low-moderate quality: search of good quality, no reporting of quality assessment • Included reviews: CS: Walters 2005, Wood-Baker 2005, Yang 2007; opioids: Jennings 2002

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
	n=59 studies				
DiSalvo 2008	• SR • Funding/CoI: not reported • Search date: not reported • Databases: MEDLINE, CINAHL, PsychINFO, Cochrane Database of systematic reviews. • Study designs: different study designs • N included studies: N=7 studies	• Eligibility criteria: patients with cancer and dyspnoea	Opioids	Narrative reporting of results	• SR of low-moderate quality: fairly broad search, language restriction (English), limitations of included studies assessed but not reported • Included studies: Jennings 2002 (SR); Mazzocato 1999, Bruera 1990, Allard 1999, Navigante 2006, Boyd 1997
Lorenz KA 2008	• SR • Funding/CoI: National Institute of Nursing Research and the Agency for Healthcare Research and Quality; CoI reported in article • Search date: April 2004 • Databases: Medline, DARE, National Consensus Project for Quality Palliative Care • Study designs: SR, RCTs • N included studies: 7 SR and 12 primary	• Eligibility criteria: patients with cancer, chronic heart failure, and dementia	Opioids	Narrative presentation of results	• SR of moderate quality: search of good quality, English only, results of quality appraisal not reported • Included studies: Jennings 2002, Booth 2004, Bruera 2003, Abernathy 2003

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
	studies on dyspnoea				
Viola R 2008	• SR • Funding/CoI: Cancer Care Ontario and the Ontario Ministry of Health and Long-Term; no CoI • Search date: mid 2006 • Databases: Medline, Cinahl, HealthSTAR, Embase, Cochrane Library, DARE; ASCO abstracts; references • Study designs: SR, RCTs • N included studies: 3 SR, 9 RCTs	• Eligibility criteria: adult patients with cancer and dyspnoea	Opiods Benzodiazepines Corticosteroids (no trials identified)	Narrative presentation of results	• SR of moderate quality: search of good quality, English only, results of quality appraisal (Jadad) not reported • Included studies: Allard 1999, Bruera 1993, Mazzocato 1999, Navigante 2006, Davis 1996, Bruera 2005; Abernathy 2003, Buck 1996, Chua 1997, Eiser 1991, Johnson 2002, Light 1989, Light 1996, Poole 1998, Woodcock 1981, Beauford 1993, Harris-Eze 1995, Jankelson 1997, Leung 1996, Masood 1995, Noseda 1997, Peterson 1996, Eimer 1985, Man 1986, Mitchell-Heggs 1980, Rice 1987

Primaire studies

Study ID	Method	Patient characteristics	Interventions	Results	Critical appraisal of study quality
Cuervo Pinna MA 2013	• Design: RCT crossover-design • Funding/CoI: report no Conflict of interests; no funding received • Setting: Palliative Care Supportive Team, Badajoz; Spain • Sample size: N=13 • Duration: During 2011;	• Eligibility criteria: patients with advanced cancer, moderate-effort dyspnoea, a Karnofsky index score greater 50 and without advanced COPD • *A priori* patient characteristics: intervention vs. control ○ Age mean 65 years ○ Around 85% male ○ Lung cancer 77% ○ Mean Dyspnoea ESAS score 6.5	Oral transmucosal fentanyl citrate (N=13) vs. Placebo (N=13)	<u>Dyspnoea</u>: 6 Minutes Walking Time; Rating on Dyspnoea Edmonton Symptom Assessment System (ESAS) Scores (n=11) At 3 min: Placebo 5.1 (2.9); Active=4.3 (2.7); p=0.13 Immediately after: Placebo 5.5 (2.8); Active=4.5 (2.0); p=0.3 30 min after: Placebo 3.4 (2.4); Active=3.0 (1.7); p=0.53 60 min after: Placebo 2.6 (2.2); Active=2.4 (1.9); p=0.56	Level of evidence: unclear risk of bias • Unclear randomization method and allocation concealment; unclear blinding

Study ID	Method	Patient characteristics	Interventions	Results	Critical appraisal of study quality
				Difference in the overall affliction score of ESAS before and after 6 minutes walking was non-significant (p=0.12) Exercise tolerance: Medium distance covered in the two periods in meters (Treatment-Effect non-significant, p=0.66): Group1 (Placebo-active, n=6): Period1=563.3 (45); Period2=528.3 (101.3) Group2 (Active-placebo, n=7): Period1=591.4 (117.5); Period2=660.7 (188.8) Difference in oxygen saturation level before/after 6minutes walking non-significant (p=0.75) Physical functioning: Not reported Quality of life: Not reported	
Gamborg H 2013	• Design: RCT • Funding/CoI: funded by "Den Faberske Fond" and "Diakonissebuset Sankt. Lukas Stiftelsen"; CoI not reported • Setting: single centre, Germany • Sample size: N=20 • Duration: recruitment Apr 2006 – Feb 2011; duration = 1h	• Eligibility criteria: dyspnoea related to advanced primary or metastatic lung cancer; resting dyspnoea intensity of at least 3 on VAS scale 0-10; regular oral or parenteral opioids for pain; no causal treatment possible; no treatment with methadone • A priori patient characteristics: intervention vs. control ○ Median age: 69 vs. 69y ○ Time from study to death: 16 vs. 45d	Red morphine drops (N=9) vs. Subcutaneous morphine (N=11)	Dyspnoea: • Severity on VAS: significant time (p=0.0451) and strong treatment effects (p<0.0001); overall VAS score was larger for red morphine drops than for SC morphine (mean t=0': 5.5 vs. 4.7; t=60': 4.4 vs. 3.0) and slightly decreasing with time Exercise tolerance: Not reported Physical functioning: Not reported Quality of life: Not reported	Level of evidence: high risk of bias • Unclear randomization method and allocation concealment • Selective reporting
Oxberry SG 2013	• Design: CCT • Funding/CoI: Clinical Research Fellowship from Hull York Medical School; no CoI • Setting: single centre, UK • Sample size: N=33 • Duration: recruitment period unclear; study duration = 4d	• Eligibility criteria: adults with CHF due to left ventricular systolic impairment (ejection fraction < 45%), NYHA class III or IV; on standard medical therapy • A priori patient characteristics: intervention vs. control ○ Mean age: 71.8 vs. 71.9y ○ Male: 10 vs. 18 ○ NYHA IV: 3 vs. 1	Opioids (N=13) vs. No opioids (N=20)	Dyspnoea: severity score • Numerical rating scale 0-10 (mean): at 3m 3.31 vs. 4.95; p=0.033 • Borg score (mean): at 3m 1.92 vs. 2.88; p=0.087 Exercise tolerance: Not reported Physical functioning: SF-12 • SF-12 physical component (mean): at 3m 34.1	Level of evidence: high risk of bias • No randomization or allocation concealment; no blinding • Open-label extension of cross-over RCT

Study ID	Method	Patient characteristics	Interventions	Results	Critical appraisal of study quality
				vs. 29.6; p=0.014 Quality of life: SF-12 • SF-12 mental component (mean): at 3m 53.2 vs. 47.1; p=0.22 • Distress (mean): at 3m 2.31 vs. 3.85; p=0.28 • Coping (mean): at 3m 8.31 vs. 7.85; p=0.38 • Satisfaction (mean): at 3m 9.00 vs. 5.95; p=0.007	
Oxberry SG 2011	• Design: cross-over RCT • Funding/CoI: funded with a Clinical Research Fellowship from Hull York Medical School; no CoI • Setting: single university centre, UK • Sample size: N=35 • Duration: recruitment Dec 2007 – May 2009; duration = 4d	• Eligibility criteria: CHF, NYHA III-IV, left ventricular systolic impairment (ejection fraction < 45%), standard medical treatment • A priori patient characteristics: ○ Mean age: 70.2y ○ Male: 86% ○ NYHA IV: 11%	Oral morphine, 5 mg, 4x/d, for 4 days vs. Oral oxycodone, 2.5 mg, 4x/d, for 4 days vs. Placebo	Dyspnoea: severity score • Numerical rating scale 0-10 (mean change from baseline): at day 4, 0.41 vs. 1.29 vs. 1.37 (NS) • Borg score (mean change from baseline): at day 4, -0.01 vs. 0.33 vs. 0.27 (NS) Exercise tolerance: Not reported Physical functioning: Not reported Quality of life: SF-12-rated quality of life did not alter for any intervention	Level of evidence: high risk of bias • Concealed allocation, blinded study • 2/37 randomized patients withdrew and were not analysed
Hui D 2014	• Design: RCT • Funding/CoI: supported by the M. D. Anderson Cancer Center Support Grant (CA 016672); no CoI • Setting: single centre, US • Sample size: N=20 • Duration: recruitment July 2012 – Dec 2012	• Eligibility criteria: adults with cancer, average intensity of breakthrough dyspnoea of at least 3/10 on a Numeric Rating Scale (NRS); Karnofsky Performance Status score of 50% or more, stable dose of strong opioids with a morphine equivalent daily dose of between 30 and 580 mg; no dyspnoea at rest of at least 7/10 • A priori patient characteristics: intervention vs. control ○ Mean age: 54 vs. 55y ○ Male: 50 vs. 40%	Placebo (N=10) vs. Subcutaneous fentanyl (N=10)	Dyspnoea: • NRS at rest before walking test (mean change from baseline): -0.7 vs. -0.9, NS Exercise tolerance: • NRS dyspnoea at the end of walking test (mean change from baseline): -2.0 vs. -1.8, NS • Walking distance at 6 min (mean change from baseline): 18.9 vs. 37.2, NS Physical functioning: Not reported Quality of life: Not reported	Level of evidence: high risk of bias • Concealed allocation, blinded study, ITT analysis • Change from baseline reported

Abbreviations: 95%CI: 95% confidence interval; CoI: conflicts of interest; COPD: chronic obstructive pulmonary disease; ITT: intention to treat; MA: meta-analysis; NRS: numeric rating scale; NS: non-significant; RCT: randomized controlled trial; RR: relative risk; SMD: standardized mean difference; SR: systematic review; VAS: visual analogue scale

References

Bailey CD, Wagland R, Dabbour R, Caress A, Smith J, Molassiotis A. An integrative review of systematic reviews related to the management of breathlessness in respiratory illnesses. BMC Pulmonary Medicine. 2010;10(63).

Ben-Aharon I, Gafter-Gvili A, Leibovici L, Stemmer SM. Interventions for alleviating cancer-related dyspnoea: a systematic review and meta-analysis. Acta Oncol. 2012;51(8):996-1008.

Cuervo Pinna et al. A randomized crossover clinical trial to evaluate the efficacy of oral transmucosal fentanyl citrate in the treatment of dysnea on exertion in patients with advanced cancer. Am J Hospice & Palliat Care 2013; nov 28 [epub ahead of print].

DiSalvo WM, Joyce MM, Tyson LB, Culkin AE, Mackay K. Putting evidence into practice: evidence-based interventions for cancer-related dyspnoea. Clin J Oncol Nurs. 2008;12(2):341-52.

Gamborg H, Riis J, Christrup L, Krantz T. Effect of intraoral and subcutaneous morphine on dyspnoea at rest in terminal patients with primary lung cancer or lung metastases. J Opioid Manag. 2013;9(4):269-74.

Hui D, Xu A, Frisbee-Hume S, Chisholm G, Morgado M, Reddy S, et al. Effects of prophylactic subcutaneous fentanyl on exercise-induced breakthrough dyspnoea in cancer patients: a preliminary double-blind, randomized, controlled trial. J Pain Symptom Manage. 2014;47(2):209-17.

Jennings AL, Davies AN, Higgins JP, Broadley K. Opioids for the palliation of breathlessness in terminal illness. Cochrane Database of Systematic Reviews. 2001;4(4):CD002066.

Lorenz KA, Lynn J, Dy SM, Shugarman LR, Wilkinson A, Mularski RA, et al. Evidence for improving palliative care at the end of life: a systematic review. Ann Intern Med. 2008;148(2):147-59.

Marciniuk DD, Goodridge D, Hernandez P, Rocker G, Balter M, Bailey P, et al. Managing dyspnoea in patients with advanced chronic obstructive pulmonary disease: a Canadian Thoracic Society clinical practice guideline. Can Respir J. 2011;18(2):69-78.

Oxberry SG, Torgerson DJ, Bland JM, Clark AL, Cleland JG, Johnson MJ. Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial. Eur J Heart Fail. 2011;13(9):1006-12.

Oxberry SG, Bland JM, Clark AL, Cleland JG, Johnson MJ. Repeat dose opioids may be effective for breathlessness in chronic heart failure if given for long enough. J Palliat Med. 2013;16(3):250-5.

Simon ST, Higginson IJ, Booth S, Harding R, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database of Systematic Reviews. 2010;1(1):CD007354.

Simon ST, Koskeroglu P, Gaertner J, Voltz R. Fentanyl for the relief of refractory breathlessness: a systematic review. J Pain Symptom Manage. 2013;46(6):874-86.

Viola R, Kiteley C, Lloyd NS, Mackay JA, Wilson J, Wong RK, et al. The management of dyspnoea in cancer patients: a systematic review. Support Care Cancer. 2008;16(4):329-37.

VRAAG 2: Niet-medicamenteuze behandeling van dyspneu?

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Bailey 2010	• SR of SRs • Funding/CoI: The Breathlessness Research Charitable Trust, UK and National Cancer Research Institute; authors have no competing interests • Search date: July 2007- September 2009 • Databases: Cochrane Library, AMED, CINAHL, EMBASE, Ovid MEDLINE, PsycINFO • Study designs: SRs • N included studies: n=59 studies	• Eligibility criteria: Adult patients with breathlessness within a wide range of non-malignant, cardiorespiratory disease	Oxygen therapies (include: ambulatory oxygen, Heliox, Oxygen during exercise training, short-burst O2 therapy, Domiciliary oxygen)	Narrative reporting	• SR of low-moderate quality: no documentation of quality appraisal • Included SRs: Ram 2002 (SR including 2 Trials), Rodrigo 2001 (SR including 2 Trials), Nonoyama 2007 (SR including 5 Trials), Bradley 2005 (SR including 31 Trials), O'Neill 2006 (SR including 8 Trials), Cranston 2005 (SR including 6 Trials), Austin 2006 (SR including 2 Trials)
			Psychologically based treatments to reduce anxiety and panic	Narrative reporting	Included SRs: Rose 2002 (SR including 6 Trials)
			Non Invasive ventilation (NIV)	Narrative reporting	Included SRs: Ram 2002 (SR including 3 Trials), Van't Hul 2002 (SR including 7 Trials), Wijkstra 2002 (SR including 4 Trials), Ram 2004 (SR including 14 Trials)

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Bausewein 2008	• SR • Funding/CoI: Funding by the Cicely Saunders Foundation, UK/ report no CoI • Search date:June2007 • Databases: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, British Nursing Index, PsycINFO, Science Citation Index Expanded, AMED, The Cochrane Pain, Palliative and Supportive Care Trials Register, The Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effectiveness • Study designs: RCTs, controlled-clinical trials • N included studies: 47 sudies	• Eligibility criteria: Adult participants suffering from breathlessness due to advanced cancer, COPD, interstitial lung disease, chronic heart failure or motor neurone disease (n=2532 participants)	Acupuncture (N=5 studies n=109 pts) vs. Placebo (sham) or usual therapy	Narrative reporting	• SR of high quality • Included RCTs: Jobst 1986, Lewith 2004, Maa 1997; Vickers 2005, Wu 2004
			Relaxation (N=4 studies, n=238pts)	Narrative reporting	• Included RCTs: Gift 1992, Louie 2004, Renfroe 1988, Yu 2007
			Walking aids (N=7 studies, n=202 pts)	Narrative reporting	• Included RCTs: Crisafulli 2007, Dalton 1995, Gupta 2006a, Gupta 2006b, Honeyman 1996, Probst 2004, Solway 2002
			Chest wall vibration (N=5 studies, n= 97 pts)	Narrative reporting	• Included RCTs: Christiano 1997, Fujie 2002, Lange 2006, Nakayama 1998, Sibuya 1994

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
			Neuromuscular electrical stimulation (N=3 studies,n= 50pts)	Narrative reporting	• Included RCTs: Bourjeily-Habr 2002, Neder 2002, Vivodtzev 2006
			Fan (N=2, n=66pts)	Narrative reporting	• Included RCTs: Baltzan 2000, Galbraith 2007
			Counselling and support (N=6 studies, n=1127)	Narrative reporting	• Included RCTs: Bredin 1999, Corner 1996
			Breathing training (N=2, n=129 pts)	Narrative reporting	• Included RCTs: Garrod 2005, Hochstetter 2005, Wu 2006
			Psychotherapy (N=2 Studies, n=85)	Narrative reporting	• Included RCTs: Eiser 1997, Rosser 1983
Ben-Aharon 2012	• SR • Funding/CoI: report no CoI • Search date: until November 2011 • Databases: CENTRAL Cochrane, MEDLINE,EMBASE, PUBMED, conference proceedings in oncology (ASCO) • Study designs: RCTs • N included studies: N=6 studies	• Eligibility criteria: Terminal cancer patients experiencing dyspnoea (n=179 pts)	Oxygen vs. No intervention, placebo, or other therapy (air or helium-enriched/ medical air)	Dyspnoea: N=6 studies SMD= -0.3 (95%CI -1.06 to 0.47) Exercise tolerance: Not reported Physical functioning: Not reported Quality of life: Not reported	• SR of moderate quality • Included RCTs: Abernathy 2010, Phillip 2006, Bruera 2003, Booth 1996, Bruera 1993, Ahmedzai 2004
			Acupuncture (N=1 Studies, n=47 pts)	Narrative reporting	• Included RCTs: Vickers 2005
Bradley 2007	• SR + MA • Funding/CoI: supported by NI Research and Development Cochrane Fellowship; no CoI • Search date: Dec 2004 • Databases: Cochrane Airways Group Specialized Register, CENTRAL, 'and other	• Eligibility criteria: RCTs comparing performance during a single exercise test using ambulatory oxygen to performance during a single exercise test with placebo air; adult patients with stable COPD	Ambulatory oxygen provided either via oxygen cylinders or a reservoir system vs. Control intervention	Dyspnoea: • Breathlessness (Borg) at isotime (4 studies, N=44): MD = -1.15 (95%CI -1.65 to -0.66) Exercise tolerance: • 6MWD (8 studies, N=238): MD = 18.86m (95%CI 13.11-24.61) • Endurance time (7 studies, N=77): MD = 2.71 min (95%CI 1.96-3.46) • Maximal distance (4 studies, N=70): MD = 32m (95%CI 20.61-43.38) Physical functioning:	• SR of moderate quality: moderate search, individual quality appraisal results not available • Included RCTs: Bradley 1978, Bye 1985, Criner 1987, Davidson 1988, Dean 1992, Eaton 2002, Fujimoto 2002, Garrod 1999, Garrod 2000, Gosselin 2004, Ishimine 1995, King 1973, Knebel 2000, Kurihara 1989, Leach 1992, Leggett 1977,

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
	databases' • Study designs: RCTs • N included studies: N=31			Not reported Quality of life: Not reported	Light 1989, Mannix 1992, Maltais 2001, McDonald 1995, McKeon 1988, O'Donnell 2001, O'Donnell 1997, Palange 1995, Raimondi 1970, Stein 1982, Somfay 2001, Swinburn 1984, Vyas 1971, Wadell 2001, Woodcock 1981
Chen 2011	• SR • Funding/CoI: not reported • Search date: January 1995 – August 2010 • Databases: MEDLINE, preMEDLINE, PubMed, EMBASE, CINAHL, Cochrane Library • Study designs: RCTs, crossover studies • N included studies: 6 studies	• Eligibility criteria: Adult, severe stable COPD-patients without reverse airflow obstruction (n=383 pts of which 307 completed the trials) • Patient characteristics: ○ Age mean=66 years ○ Predominantly male ○ Follow up 3 months to 2.2 years	Nocturnal Non-invasive positive pressure ventilation (NIPPV) for at least 3 months vs. Identical treatment apart from NIPPV	Dyspnoea: Narrative reporting only Exercise tolerance: Mainly narrative reporting apart from a combination of three studies: 6MWD: WMD= -13.95; 95%CI: (-57.74, 29.84) Physical functioning: Not reported Quality of life: Not reported	• SR of high quality • Included RCTs: Casanova 2000, Clini 2002, Duiverman 2008, Gay 1996, McEvoy 2009, Meecham 1995
Cranston 2008	• SR • Funding/CoI: Authors declare no CoI • Search date: April 2006 • Databases: OVID MEDLINE, EMBASE, Australasian Medical index, Cochrane reviews, CENTRAL, CINAHL, Cancer Lit, ACP Journal Club, TRIP, Dissertation Abstracts, LILACS, LOCATOR plus, PubMed • Study designs: RCTs, unblinded studies allowed • N included studies: N=8 studies	• Eligibility criteria: Adults with chronic end-stage disease (n=144) • Patient characteristics: ○ 97 cancer patients, 35 cardiac failure, 12 kyphoscoliosis ○ Mostly males	Oxygen therapy administered in non-acute care setting vs. Breathing room air/ placebo	Dyspnoea: In cancer patients: VAS-differences: Air-Baseline: -0.78; 95%CI: (-20.77, 19.21) Oxygen – Baseline:-11.79 ; 95%CI: (-16.98; -6.59) Oxygen – Air:-12.20; 95%CI: (--29.32,4.93) Hypoxaemia-Baseline: -11.06; 95%CI: (-16.94; -5.17) Oxygen vs. Air Patient-perceived change at rest: Peto-OR: 4.94; 95%CI: (1.48; 16.43) Results from Individual study (N=1) Patients with SaO2<=90%: -18.0; 95%CI: (-29.87;-6.13) Exercise tolerance: In Cancer Patients: Oxygen minus Air VAS after 6MW: -7.10; 95%CI: (-16.34; 2.14) Oxygen minus Air Distance (in meters): 22.47; 95%CI: (-21.49; 66.43) Individual study (N=1) Oxygen vs. Air Patient-perceived change post 6 minute walk:	• SR of high quality • Included RCTs: Ahmedzai 2004, Booth 1996, Bruera 1993, Bruera 2003, Chua 1996, Meecham Jones 1995, Moore 1992, Restrick 1992

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				Peto-OR 2.62; 95%CI: (1.00;6.85) Oxygen minus Air Respiratory rate post 6 minute-walk: -2.10; 95%CI: (-3.91;-0.29) Oxygen minus Air 3-minutes walk numerical rating scale: -1.0; 95%CI: (-11.20;9.20) Oxygen minus Air after 6MW Borg score: -0.2; 95%CI: (-1.86;1.46) Oxygen minus Air fatigue score after 6MW: -0.30; 95%CI -1.48 to 0.88 In Cardiac-failure patients: Oxygen minus Air 3 minutes exercise (treadmill or cycle): -0.58; 95%CI -2.00 to 0.84 Oxygen minus Air Borg or VAS score after 6 minutes treadmill and cycle exercise: -1.09; 95%CI -1.74 to -0.44 Oxygen minus Air VAS or Borg at peak exercise: -1.06; 95%CI: (-3.14;1.02) Minute ventilation, peak exercise: -6.68; 95%CI: (-11.89, -1.48) Individual Study (N=1) Oxygen minus Air Borg 3 minutes treadmill exercise: 0.16; 95%CI: (-0.67; 0.99) Oxygen minus Air VAS score 3 minutes cycle ergometer exercise: -1.29; 95%CI:(-2.04,-0.54) Oxygen minus Air Borg score after 6 minutes treadmill exercise: -0.85; 95%CI: (-1.64;-0.06) Oxygen minus Air VAS score after 6 minutes cycle exercise: -1.57; 95%CI: (-2.70;-0.44) Oxygen minus Air Borg score at peak treadmill exercise: 0.08; 95%CI: (-1.56;1.72) Oxygen minus Air VAS score at peak cycle exercise: -2.05; 95%CI: (-3.25;-0.85) Oxygen minus air fatigue after 3 minutes exercise: -0.08; 95%CI:(-0.95;0.79) Oxygen minus air fatigue after 6 minutes exercise: -0.21; 95%CI: (-1.37;0.95) Oxygen minus air fatigue at peak exercise: 0.21; 95%CI: (-1.33;1.75) Oxygen minus Air within patient change in exercise duration (seconds) 52.00; 95%CI: (36.69;67.31) <u>Physical functioning</u>: Not reported <u>Quality of life</u>: Not reported	

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
DiSalvo 2008	• SR • Funding/CoI: not reported • Search date:not reported • Databases: MEDLINE, CINAHL, PsychINFO, Cochrane Database of systematic reviews. • Study designs: different study designs • N included studies: N=7 studies	• Eligibility criteria: Patients with cancer and dyspnoea	Oxygen	Narrative reporting	• SR of low-moderate quality: fairly broad search, language restriction (English), limitations of included studies assessed but not reported • Included RCTs: Bruera 1993, Bruera 1993b, Ahmedzai 2004
			Cognitive-Behavioural approach	Narrative reporting	• Included studies: Bredin 1999, Corner 1996, Hately 2003
			Acupuncture	Narrative reporting	• Included studies: Filshie 1996
Holland 2012	• SR • Funding/CoI: Internal: La Trobe University, Australia; report no CoI • Search date: until October 2011 • Databases: Cochrane CENTRAL, MEDLINE, EMBASE, CINAHL, AMED, PsycINFO, PEDro database • Study designs: randomised parallel trials, RCTs • N included studies: N=16 studies	• Eligibility criteria: Adults with chronic obstructive pulmonary disease in stable condition • Patient characteristics: ○ Range of mean age 51 to 73	Pursed lip breathing	<u>Dyspnoea</u>: Measured within QoL (Dyspnoea): -12.94; 95%CI: (-22.29; -3.60) Individual studies (N=1): Pursed lip breathing vs. no breathing retraining: Breath Questionnaire (after 4 weeks) difference: -4.0; 95%CI (-20.40,12.40) (N=1) Breath Questionnaire (after 12 weeks) difference: -10.00; 95%CI (-28.98;8.89) (N=1) Medical Research Council Score (at week 8) difference: -1.0; 95%CI (-1.73;-0.27) Pursed lip breathing vs. no expiratory muscle training Breath Questionnaire (at 4 weeks) difference: -3.0; 95%CI(-19.62;13.62) Breath Questionnaire (at 12 weeks) difference: -9.0; 95%CI(-28.41;10.41) <u>Exercise tolerance</u>: Additional reporting about individual studies (N=1) Pursed lip breathing vs. usual care Borg Score after 6 MWT (after 4 weeks) difference: 0.0; 95%CI (-0.76,0.76) (N=1) Borg Score after 6MWT (after 12 weeks) difference: -1.00; 95%CI (-2.10;0.10) (N=1)	• SR of high quality • Included RCTs: Nield 2007, Zhang 2008, Wu 2006, Li 2002, Chan 2011

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				Pursed lip breathing vs. no breathing retraining Exercise capacity 6MWT (at 8 week) difference: 50.10; 95%CI (37.21;62.99) Pursed lip breathing vs. no expiratory muscle training Borg Score after 6 MWT (at 4 weeks) difference: -0.50; 95%CI (-1.26;0.26) (N=1) Borg Score after 6MWT (at 12 weeks) difference: -0.90; 95%CI (-1.71;-0.09) (N=1) Physical functioning: Not reported Quality of life: Pursed lip breathing vs. no expiratory muscle training QoL, Hiratsuka scale: 0.85; 95%CI: (-3.03, 4.73) Individual study (N=1): Cai Scale QoL: -0.27; 95%CI (-0.40;-0.14)	
			Diaphragmatic breathing	Dyspnoea: Individual reporting study (N=1) Diaphragmatic breathing vs. no breathing retraining Medical Research Council Score (at week 4) difference: -0.27; 95% (-0.76; 0.22) Exercise tolerance: Individual reporting study (N=1) Diaphragmatic breathing Vs. no breathing retraining Exercise capacity change in 6MWT (at week 4) difference: 34.67; 95%CI (4.05;65.29) Physical functioning: Not reported Quality of life: Individual reporting study (N=1) Diaphragmatic breathing Vs. no breathing retraining QoL change in SGRQ (at week 4): -10.51; 95%CI (-17.77;-3.25)	• Included studies: Lausin 2009, Yamaguti 2012, Noseda 1987
			Yoga vs. no breathing retraining	Dyspnoea: Narratively reported Exercise tolerance: Exercise capacity change in 6Minutes Walking Time at 3 months: 44.51; 95%CI: (28.47; 60.55) Individual reporting study (N=1): Dyspnoea intensity at the end of 6MWT difference: 0.50;	• Included studies: Donesky_nCuenco 2009, Katiyar 2006

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				95%CI (-0.99;1.99) Dyspnoea intensity at the end of incremental cycle ergometer test difference: 0.60; 95%CI (-0.98;2.18) Dyspnoea distress at the end of 6MWT difference: 0.20; 95%CI (-0.97;1.37) Dyspnoea distress at the end of incremental cycle ergometer test difference: 0.50; 95%CI (-1.60;2.60) Peak work on incremental cycle ergometry: 15.00; 95%CI (-3.16;33.16) Physical functioning: Not reported Quality of life: Individual study (N=1) QoL at 12 week: 1.60; 95%CI (-3.10, 6.30) QoL change in St Georges Respiratory Questionnaire: -5.30; 95%CI (-7.82;2.78)	
			Other breathing retraining vs. no breathing retraining	Dyspnoea: Individual study (N=1) MRC scale difference: -1.46; 95%CI (-2.19;-0.73) Exercise tolerance: Individual study (N=1) Exercise capacity 6MWT (at 8 weeks) difference: 50.10; 95%CI (37.21;62.99) Exercise capacity 6MWT (at 8 weeks) difference: 88.20; 95%CI (75.28;101.12) Physical functioning: Not reported Quality of life: Individual study (N=1) QoL at 8 weeks difference: -18.10; 95%CI (-30.66;-5.54)	• Included studies: Chauhan 1992, Saunders 1965, Zhang 2008, Sun 2003, Yan 1996

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
			Ventilation feedback training (plus exercise)	Dyspnoea: Ventilation feedback training vs. exercise alone As part of QoL: 0.03; 95%CI: (-0.43; 0.49) Exercise tolerance: Individual reporting study (N=1) Ventilation feedback training vs. exercise alone Duration of constant work rate exercise at 15 weeks difference: 8.50; 95%CI (-4.38;21.38) Exercise capacity change in 6MWT (at 4 weeks) difference: -12.58; 95%CI (-35.93; 10.77) Dyspnoea at isotime on constant work rate treadmill test difference: -0.90; 95%CI (-2.25; 0.45) Change in Borg Score at the end of 6MWT difference: -0.40; 95%CI (-1.26;0.46) SpO2 at isotime during constant work rate cycle test difference: 0.90; 95%CI (-1.19;2.99) Oxygen consumption isotime during constant work rate test difference: -1.30; 95%CI (-3.38;0.78) Respiratory rate at isotime on constant work rate treadmill test difference: -6.00; 95%CI (-9.27;-2.73) Inspiratory time at isotime on constant work rate treadmill test difference: 0.08; 95%CI (-0.06;0.22) Expiratory time at isotime on constant work rate treadmill test difference: 0.43; 95%CI (0.18; 0.68) Ventilation feedback training vs. exercise training Duration of constant work rate exercise at 15 weeks difference: -15.40; 95%CI (-28.10;-2.70) Dyspnoea at isotime on constant work rate treadmill test difference: 1.10; 95%CI (-0.71; 2.91) SpO2 at isotime during constant work rate cycle test difference: 0.50; 95%CI (-1.62;2.62) Minute ventilation at isotime during constant work rate treadmill test difference: -3.70; 95%CI (-11.62;4.22) Respiratory rate at isotime on constant work rate treadmill test difference: -2.00; 95%CI (-6.90;2.90) Inspiratory time at isotime on constant work rate treadmill test difference: 0.07; 95%CI (-0.09;0.23) Expiratory time at isotime on constant work rate treadmill test difference: 0.27; 95%CI (-0.06; 0.60) Physical functioning: Not reported Quality of life:	• Included studies: Collins 2008, van Gestel 2011

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				Ventilation feedback training vs. exercise alone QoL Questionnaire difference: 0.03; 95%CI (-0.43;0.49)	
			Pursed Lip breathing, diaphragmatic breathing and nutritional supplementation vs. usual care	Dyspnoea: Not reported Exercise tolerance: Not reported Physical functioning: Not reported Quality of life: Individual reporting study (N=1) QoL Cai Questionnaire difference: -0.43; 95%CI (-0.69;-0.17)	Included study: Li 2002
			Pursed Lip breathing, diaphragmatic breathing and respiratory muscle gymnastics vs. no breathing retraining	Dyspnoea: Not reported Exercise tolerance: Not reported Physical functioning: Individual reporting study (N=1) Change in inspiratory muscle strength difference: -1.39; 95%CI (-1.76;-1.02) Change in expiratory muscle strength difference: 2.72; 95%CI (2.09;3.35) Change in Pdi difference: 0.52; 95%CI (0.13;0.91) Chane in maximal Pdi difference: 2.48; 95%CI (1.61; 3.35) Quality of life: Not reported	Included Study: Yan 1996

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
			Pursed Lip breathing, diaphragmatic breathing and walking vs. usual care	Dyspnoea: Not reported Exercise tolerance: Not reported Physical functioning: Not reported Quality of life: Individual study (N=1) QoL St Georges Respiratory Questionnaire difference: -0.60; 95%CI (-4.77;3.57)	Included Study: Chan 2011
Kolodziej 2007	• SR • Funding/CoI: no funding reported; CoI none declared • Search date: until 2003 • Databases: MEDLINE, EMBASE, CINAHL, Conference Papers Index, Cochrane Library, Online Computer Library Centre, American College of Physicians Journal Club, PubMed, Biological Abstracts and Dissertation Abstracts, American Journal of Respiratory and Critical Care Medicine, Chest, European Respiratory Journal, Lung, The New England Journal of Medicine and Thorax. • Study designs: RCTs, crossover-trials • N included studies: N=15	• Eligibility criteria: Adults with severe, stable chronic obstructive pulmonary disease and chronic respiratory failure(n=466 pts) • Patient characteristics: ○ Mean age 63 (44-74) ○ Follow-up: RCTs: 5 days- 2yrs; 3 non-RCTs: 1-3days; 3 non-RCTs: 6weeks – 6 months	Bilevel Noninvasive positive pressure ventilation (NIPPV) Vs Spontaneous breathing, sham ventilation, Long-term oxygen therapy, exercise	Dyspnoea: Each RCT demonstrated an improvement: narrative reporting. Exercise tolerance: 6MWT narrative reporting Physical functioning: Narrative reporting Quality of life: Narrative reporting	• SR of moderate quality • Included RCTs: Casanova 2000, Clini 2002, Diaz 2002, Garrod 2000, Gay1996, Renston 1994, Meecham Jones 1995, Strumpf 1991 • Included non-RCTs: Ambrosino 1992, Krachman1997, Lien 1993, Lin 1996, Maragoni 1997, Nava 1993, Highcock 2003

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Lee 2011	• SR • Funding/CoI: In part supported by a grant to the University of Kentucky from the National Institutes of Health's National Institute of Nursing Research; authors declare no CoI • Search date:January2000-January2010 • Databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, PubMed • Study designs: RCTs, review of studies • N included studies: N=2 (out of 43) studies	• Eligibility criteria: Patients with Chronic obstructive pulmonary disease	Acupressure Vs Placebo	Dyspnoea: Pulmonary function status, Dyspnoea Questionaire (n=1 stdy), mean(SD): Acupressure: 0.98(1.41) vs. Control: 0.41 (43); Effect size 0.55: 95%CI: (-0.01,1.14); p<0.05 VAS-Scale, pre-post, mean (SD): Acupressure: 69.4 (12.0) vs. Control: 62.7 (12.03); Effect size 0.56: 95%CI: (-0.01,1.10); p<0.05 Exercise tolerance: Narrative reporting: improvement of six-minute walking distance Physical functioning: Narrative reporting: improvement of pulmonary function, oxygen saturation, blood pressure, heart rate, respiratory rate Quality of life: Narrative reporting: improvement of state-anxiety	• SR of moderate quality • Included RCTs: Wu 2004, Tsay 2005
Marciniuk 2011	• SR / Guideline • Funding/CoI: NO external funding source/ online-declaration of CoI • Search date: January1996-March2009 • Databases: Medline, Embase, The Cochrane Library, the Canadian Medical Association InfoBase and the National Guideline Clearinghouse. • Study designs: Different study types • N included studies: N=35 studies	• Eligibility criteria: Patients with advanced chronic obstructive pulmonary disease (COPD) experiencing dyspnoea	Chest vibration techniques	Narrative reporting	• SR of moderate quality: no search strategy provided, unclear how quality appraisal was done • Included Studies: Christiano 1997, Fuje 2002

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
			Neuromuscular electrical muscle stimulation	Narrative reporting	• Included studies: Bourjeily-Habr 2002, Neder 2002, Vivodtzev 2006
			Walking aids	Narrative reporting	• Included studies: Crisafulli 2007, Gupta 2006a, Gupta 2006b, Honeyman 1996, Probst 2004, Solway 2002
			Breathing exercises (purst-lips breathing, singing)	Narrative reporting	• Included studies: Faager 2008, Garrod 2005, Nield 2007, Spahija 2005
			Behavioural techniques	Narrative reporting	• Included studies: Davis 2006, Kunik 2008, Lomundal 2007
			Counselling disease management projects	Narrative reporting	• Included studies: Niesink 2007, Ketelaars 1998
			Relaxation techniques (55)	Narrative reporting	• Included studies: Louie 2004
			Oxygen therapy	Narrative reporting	• Included studies: Lilker 1975, Heaton 1983, Okubadejo 1996, Eaton 2004, Lahdensuo 1989, Crockett 1999, McDonald 1995, Eaton 2002, Nonoyama 2007, Moore 2011, Lacasse 2005, Sandland 2008
Norweg 2013	• Non-systematic review • Funding/CoI: Funding not reported/ authors declare no CoI • Search date:1996-2013 • Databases: not reported • Study designs: RCTs • N included studies: N=23 studies	• Eligibility criteria: Patients with chronic obstructive pulmonary disease with dyspnoea	Meditation	Narrative reporting	• SR of low quality • Included RCTs:Donesky-Cuenco 2009, Yeh 2010, Chan 2011, Ng 2011, Mularski 2009, Katiyar 2006

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
			Cognitive-behavioural therapy (psychotherapy)	Narrative reporting	• Included studies: Livermore 2010, Kunik 2008
			Breathing exercises	Narrative reporting	• Included studies:Yamaguti 2012, Nield 2004, Nield 2007,Collins 2008, Bonilha 2009, van Gestel 2012, Scherer 2000
Osadnik 2012	• SR • Funding/CoI: Canada Research Chairs Program, Canada/ Three authors conduct a study which may be included in future updates • Search date: October 2011 • Databases: CAGR, CENTRAL,MEDLINE, EMBASE, CINAHL, AMED, PsycINFO, handsearching respiratory journals and meeting abstracts • Study designs: RCTs, RXTs • N included studies: N=28	• Eligibility criteria: People with acute exacerbations of chronic obstructive pulmonary disease (COPD) and stable COPD and without bronchiectasis or asthma (n=278 pts)	Treatment using airway clearance techniques (ACTs, including 'conventional ' techniques, breathing exercises and PEP or mechanical devises) vs. no intervention, sham or coughing alone	<u>Dyspnoea</u>: Acute Patients: Individual study (N=1) Non-PEP techniques: Borg scale difference: -1.30; 95%CI (-2.14;-0.46) Stable Patients: Individual study (N=1) PEP techniques: Borg scale difference: -0.30; 95%CI (-0.53;-0.07) <u>Exercise tolerance</u>: Stable Patients: PEP-Techn. Exercise tolerance 6MWD difference: 12.93; 95%CI (5.98;19.89) Individual study (N=1) PEP-Techn. Exercise tolerance 12MWD difference: 111.00; 95%CI (66.46;155.54) <u>Physical functioning</u>: Not reported <u>Quality of life</u>: Acute Patients: Individual study (N=1) Non-PEP techniques: QoL-SGRQ difference: -2.3; 95%CI (-11.8;7.20) Stable Patients: Individual study (N=1) PEP techniques: QoL-SGRQ difference: -6.10; 95%CI (-8.93;-3.27)	• SR of high quality • Included RCTs: Bellone 2002, Brown 1987, Cegla 1997, Cegla2002, Christensen 1990, Christensen 1991, Haidl 2002, Inal-Ince 2004, Kodric 2009, May 1979, Morsch 2008, Newton 1978, Oldenburg 1979, Pavia 1976, Vargas 2005, Weiner 1996, Wolkove 2002, Wolkove 2004; Anthonisen 1964, Celga 2001, Christensen 1991a, Hasani 1995, Martins 2006, Martins 2007, Newton 1978a, Rasmussen 2001, Rivington-Law 1984, van Hengstum 1988
Pan 2014	• SR + MA • Funding/CoI: not reported • Search date: Dec 2012 • Databases: PubMed,	• Eligibility criteria: patients with COPD	Neuromuscular electrical stimulation of the lower limbs	<u>Dyspnoea</u>: 3 studies WMD = -0.98; 95%CI -1.42 to -0.54; p<0.0001 <u>Exercise tolerance</u>: 6MWD, 2 studies WMD = 13.63m; 95%CI -17.39 to 44.65; p=0.39; I^2 51%	• SR of moderate quality • English articles only • Included RCTs: Bourjeily-Habr 2002, Neder 2002, Zanotti 2003, Vivodtzev 2006, Dal Corso 2007,

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
	Embase • Study designs: RCTs • N included studies: N=8			Physical functioning: Not reported Quality of life: Not reported	Napolis 2011, Abdellaoui 2011, Vivodtzev 2012
Struik 2013	• SR + MA • Funding/CoI: no CoI • Search date: Aug 2012 • Databases: Medline, Embase, CENTRAL, CINAHL, AMED, PsycINFO, respiratory journals, meeting abstracts; references; authors • Study designs: RCTs • N included studies: N=7	• Eligibility criteria: patients with COPD	NIPPV, applied through a nasal or facemask, for at least five hours during the night, for at least three consecutive weeks	Dyspnoea: • at 3m (2 studies, N=71): results not reported • at 12m (1 study, N=90): results not reported Exercise tolerance: 6MWD • at 3m (3 studies, N=40): MD = 27.7; 95%CI -11.0 to 66.3 • at 12m (1 study, N=46): MD = 3.2; 95%CI -49.7 to 56.1 Physical functioning: Not reported Quality of life: • at 3m (1 study, N=18): results not reported • at 12m (2 studies, N=103): SGRQ, MD = 0.90; 95%CI -19.21 to 21.01	• SR of high quality, IPD analysis • Included RCTs: Casanova 2000, Clini 2002, Gay 1996, McEvoy 2009, Meecham Jones 1995, Sin 2007, Strumpf 1991
Towler 2013	• Integrative overview of reviews • Funding/CoI: One author supported by scholarship from Cancer Experience Collaborative funded by National Cancer Research Institute; No relevant financial CoI • Search date:2000 to August 2011 • Databases: MEDLINE, EMBASE, AMED, CINAHL, Web of Science, Cochrane Library, British Nursing Index, Index to Theses, Dissertations and Theses and NHS evidence. • Study designs: • N included studies: N=3 (out of17) studies	• Eligibility criteria: Human adults >17 with cancer	Acupuncture	Narrative reporting	• SR of moderate quality • Included reviews: Cohen 2005, Standish 2008, O'Regan 2010

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Uronis 2011	• SR • Funding/CoI: Agency for Healthcare Research and Quality, USA/ declare no CoI. • Search date: November 2009 • Databases: Cochrane Airways Group Specialised Register of trials including CENTRAL, MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, handsearching respiratory journals and meeting abstracts • Study designs: RCTs • N included studies: N=28 studies	• Eligibility criteria: Mildly or non-hypoxaemic adult patients with chronic obstructive pulmonary disease with breathlessness (n=702 pts)	Oxygen (Long-term therapy) Vs. Medical air	<u>Dyspnoea</u>: Breathlessness SMD -0.37; 95%CI (-0.50;-0.24) Subgroup analysis- study focus sensation: Breathlessness SMD -0.39; 95%CI (-0.66;-0.12) Subgroup analysis- study focus function: Breathlessness SMD -0.45; 95%CI (-0.61;-0.30) Subgroup analysis- study focus both: Breathlessness SMD -0.32; 95%CI (-0.67;-0.03) Subgroup analysis- not using short-burst: Breathlessness SMD -0.46; 95%CI (-0.59;-0.33) Subgroup analysis- using short-burst: Breathlessness SMD 0.01; 95%CI (-0.26;0.28) Subgroup analysis- exertional desaturation: Breathlessness SMD -0.33; 95%CI (-0.46;-0.20) Subgroup analysis- no exertional desaturation: Breathlessness SMD -0.69; 95%CI (-1.04;-0.34) Subgroup analysis- mean PaO2>=70mmHg: Breathlessness SMD -0.42; 95%CI (-0.60;-0.24) Subgroup analysis- mean PaO2<70mmHg: Breathlessness SMD -0.25; 95%CI (-0.50;0.00) Breathlessness-sensitivity analysis-quality SMD -0.25; 95%CI (-0.55;0.06) Breathlessness-sensitivity analysis-no imputed quantities SMD -0.36; 95%CI (-0.64;-0.09) Breathlessness-sensitivity analysis-no outliers SMD -0.33; 95%CI (-0.45;-0.22) Breathlessness-sensitivity analysis-no end exercise SMD -0.37; 95%CI (-0.54;-0.21) Breathlessness-subgroup analysis-short burst or not-post hoc-no outliers SMD -0.33; 95%CI (-0.45;-0.22) Subgroup analysis- not using short-burst: Breathlessness SMD -0.42; 95%CI (-0.55;-0.28) Subgroup analysis- using short-burst: Breathlessness SMD -0.03; 95%CI (-0.28;0.22) Breathlessness-subgroup analysis-study focus-post hoc-no outliers SMD -0.33; 95%CI (-0.45;-0.22) Subgroup analysis- study focus= function: Breathlessness SMD -0.41; 95%CI (-0.58;-0.25) Subgroup analysis- study focus= sensation: Breathlessness SMD -0.39; 95%CI (-0.66;-0.12) Subgroup analysis- study focus= both: Breathlessness SMD -0.15; 95%CI (-0.43;0.14)	• SR of high quality • Included RCTs: Davidson 1988, Dean 1992, Eaton 2002, Eaton 2006 ,Eves 2006, Garrod 1999, Ishimine 1995, Killen 2000, Knebel 2000, Kurihara 1989, Laude 2006, Leach 1992, Lewis 2003, Maltais 2001, McDonald 1995, McKeon 1988a, McKeon 1988b, Moore 2009, Nandi 2003, O'Donnell 1997, Somfay 2001, Swinburn 1984, Woodcock 1981, Emtner 2003, Haidl 2004, Rooyackers 1997, Wadell 2001, Jolly 2001

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				Breathlessness-subgroup analysis-saturation on exertion-post hoc-no outliers SMD -0.33; 95%CI (-0.45;-0.22) Subgroup analysis- no exertional desaturation: Breathlessness SMD -0.57; 95%CI (-0.95;-0.19) Subgroup analysis- exertional desaturation: Breathlessness SMD -0.31; 95%CI (-0.42;-0.18) Breathlessness-subgroup analysis-mean PaO2-post hoc-no outliers SMD -0.33; 95%CI (-0.45;-0.22) Subgroup analysis- mean PaO2>=70: Breathlessness SMD -0.36; 95%CI (-0.51;-0.22) Subgroup analysis- mean PaO2<70: Breathlessness SMD -0.25; 95%CI (-0.50;0.00) Breathlessness-post hoc-no short-burst studies SMD -0.46; 95%CI (-0.59;-0.33) Breathlessness- post hoc-subgroup analysis- saturation on exertion- no short burst SMD -0.46; 95%CI (-0.59;-0.33) Subgroup analysis- with exertional desaturation: Breathlessness SMD -0.43; 95%CI (-0.57;-0.29) Subgroup analysis- with no exertional desaturation: Breathlessness SMD -0.69; 95%CI (-1.04;-0.34) Breathlessness- post hoc-subgroup analysis- study focus-no short burst SMD -0.53; 95%CI (-0.69;-0.36) Subgroup analysis- focus=sensation: Breathlessness SMD -0.42; 95%CI (-0.71;-0.13) Subgroup analysis- focus=function: Breathlessness SMD -0.53; 95%CI (-0.74;-0.33) Subgroup analysis- focus=both: Breathlessness SMD -0.67; 95%CI (-1.19;-0.14) Breathlessness- post hoc-subgroup analysis- mean PaO2-no short burst SMD -0.46; 95%CI (-0.58;-0.33) Subgroup analysis- mean PaO2 >=70: Breathlessness SMD -0.47; 95%CI (-0.62;-0.32) Subgroup analysis- mean PaO2<70: Breathlessness SMD -0.43; 95%CI (-0.67;-0.19) Breathlessness- post hoc-sensitivity analysis- quality- no short burst SMD -0.25; 95%CI (-0.59;0.09) Breathlessness- post hoc-no outliers and no short burst SMD -0.42; 95%CI (-0.55;-0.28) Breathlessness- post hoc-sensitivity analysis-no imputed quantities and no outliers SMD -0.31; 95%CI (-0.56;-0.05) Breathlessness- post hoc-sensitivity analysis-no end	

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				exercise and no outliers SMD -0.31; 95%CI (-0.44;-0.18) Breathlessness- subgroup analysis-dyspnoea measure SMD Modified Borg -0.44; 95%CI (-0.58;-0.29) Breathlessness- subgroup analysis-dyspnoea measure SMD VAS -0.25; 95%CI (-0.48;-0.02) Breathlessness- subgroup analysis-dyspnoea measure SMD VAS and Borg -0.37; 95%CI (-0.50;-0.24) Exercise tolerance: Not reported Physical functioning: Not reported Quality of life: Not reported	
Uronis 2008	• SR • Funding/CoI: Uronis salary supported by the Agency for Healthcare Research and Quality/ CoI not reported • Search date:1966 to December 2006 • Databases: MEDLINE, EMBASE, handsearch of reference lists. • Study designs: • N included studies: N=5 studies	• Eligibility criteria: Mildly hypoxaemic or non-hypoxaemic adult cancer patients with dyspnoea not qualifying for home oxygen therapy • • Patient characteristics: ○ Age median= 65 years ○ 39% females	Oxygen (administered by a non-invasive method; one study used Heliox28) Vs Medical air	Dyspnoea: VAS or comparable scale (n=4 stds) SMD= -0.09: 95%CI: (-0.22, 0.04); p=0.16 Exercise tolerance: 6MWT: Narrative reporting only; one study reports significant increase in walking distance while another study found no difference Physical functioning: not reported Quality of life: not reported	• SR of moderate quality • Included RCTs: Buera 1993, Bruera 2003, Booth 1996, Ahmedzai 2004, Philip 2006

Primaire studies

Study ID	Method	Patient characteristics	Interventions	Results	Critical appraisal of study quality
Barton 2010	• Design: RCT • Funding/CoI: Marie Curie Cancer Care SuPaC CBG grant 15; no CoI • Setting: single tertiary centre study, UK	• Eligibility criteria: adults with refractory breathlessness caused by malignant lung disease (due to primary or secondary tumours), an expected prognosis of at least 3m and a KPS of >40%	Three sessions of breathing training (N=11) vs. Single session of	Dyspnoea: mean change from baseline to week 4 • Breathlessness severity (NRS): -2.5 vs. 0.8, SD 3.2, effect size 1.0 • Worst breathlessness (NRS): -3.0 vs. -1.0, SD 2.5, effect size 0.8 Exercise tolerance:	Level of evidence: high risk of bias • Unblinded pilot study • Selective reporting: no estimates of statistical significance; change from

Study ID	Method	Patient characteristics	Interventions	Results	Critical appraisal of study quality
	• Sample size: N=22 • Duration: recruitment Sept 2007 – Aug 2008; follow-up for 8 weeks	• *A priori* patient characteristics: intervention vs. control ○ Mean age: 71y ○ Men: 41%	breathing training (N=11)	Not reported Physical functioning: Not reported Quality of life: • EQ-VAS: appeared to improve in the three session group but stable in the single-group • EQ-5D: not interpretable on so few data	baseline reported • No ITT analysis, only 11/22 patients included
Bausewein 2010	• Design: RCT • Funding/CoI: supported by the charity Cicely Saunders International; no CoI • Setting: 3 centres, Germany • Sample size: N=70 • Duration: data collection June 2006 – Nov 2007	• Eligibility criteria: patients with advanced malignant disease (primary lung cancer or secondary lung metastases/ lung involvement due to cancer) or COPD stage III/IV • *A priori* patient characteristics: intervention vs. control ○ Age: 64.5 vs. 66.6y ○ Male: 19 vs. 17 ○ COPD: 24 vs. 21	Handheld fan directed to the face (N=38) vs. Wristband (N=32)	Dyspnoea: Borg score • Mean change: 0.6 vs. 0.8, p=0.90 Exercise tolerance: Not reported Physical functioning: Not reported Quality of life: Not reported	Level of evidence: high risk of bias • Phase II trial • No blinding possible • No ITT-analysis: only 36/70 patients included in analysis
Dreher 2009	• Design: cross-over RCT • Funding/CoI: open research grant from Breas Medical AB, Mölnlycke, Sweden; no CoI • Setting: single university centre, Germany • Sample size: N=19 • Duration: recruitment period unclear	• Eligibility criteria: stable COPD stage IV, dyspnoea during mild exertion • *A priori* patient characteristics: ○ Age: 63y ○ Male: 10/11 ○ FEV1 % predicted: 26%	Single dosage of O2 vs. Double dosage of O2 vs. NPPV in addition to single dosage of O2 All during walking	Dyspnoea: Borg scale • During 12MWT: median increase 4 vs. 3 vs. 4; p=0.266 Exercise tolerance: • 6MW distance: 311 vs. 322 vs. 284m, p=0.01 • 12MW distance: 619 vs. 622 vs. 555m; p=0.024 Physical functioning: Not reported Quality of life: Not reported	Level of evidence: high risk of bias • Unclear randomization method and allocation concealment; blinding not mentioned, but probably not possible • Only 11/19 patients included in analysis
Duiverman 2011	• Design: RCT • Funding/CoI: funded by the Dutch Asthma Foundation; one author received grants from Respironics • Setting: single university centre, the Netherlands • Sample size: N=72 • Duration: recruitment period unclear; follow-up of 2y	• Eligibility criteria: COPD stage III-IV, age 40-76y, stable clinical condition, chronic hypercapnic respiratory failure • *A priori* patient characteristics: intervention vs. control ○ Mean age: 63 vs. 61y ○ Male: 16 vs. 17	Nocturnal NPPV + rehabilitation (N=37) vs. Rehabilitation only (N=35)	Dyspnoea: • MRC dyspnoea score: adjusted difference in change – mean = -0.4 (95%CI -0.8 to 0.0; p<0.05) • CRQ dyspnoea: adjusted difference in change – mean = -1.7 (95%CI -4.8 to 1.5) Exercise tolerance: • 6MW distance: difference in change = 77.3m (95%CI 46.4-108.0; p<0.001)	Level of evidence: high risk of bias • Concealed allocation • No blinding • No ITT-analysis: several drop-outs, not included in analysis

Study ID	Method	Patient characteristics	Interventions	Results	Critical appraisal of study quality
				Physical functioning: • GARS: adjusted difference in change – mean = -3.8 (95%CI -7.4 to -0.4; p<0.05) • SRI physical functioning domain: difference = 10.7% (95%CI 3.8 to 17.6; p=0.003) Quality of life: • CRQ total: adjusted difference in change – mean = -1.3 (95%CI -9.7 to 7.4) • MRF-28 total: difference in change = -13.4% (95%CI -22.7 to -4.2; p=0.005)	
Hui 2013	• Design: RCT • Funding/CoI: M.D. Anderson Cancer Center Support Grant (CA 016672); no CoI • Setting: single cancer centre, US • Sample size: N=30 • Duration: recruitment Feb 2007 – Apr 2011; follow-up duration unclear	• Eligibility criteria: 18+, diagnosis of advanced cancer (locally advanced, recurrent, or metastatic disease), average intensity of dyspnoea at rest over the past week >=3/10 on (NRS) despite supplemental oxygen; life expectancy >1w • *A priori* patient characteristics: intervention vs. control ○ Mean age: 63 vs. 59y ○ Male: 57 vs. 37%	BiPAP (N=14) vs. High-flow oxygen (N=16)	Dyspnoea: mean change • NRS: -3.2 vs. -1.9, p=0.32 • Modified Borg scale: -1.5 vs. -2.1, p=0.29 Exercise tolerance: Not reported Physical functioning: Not reported Quality of life: Not reported	Level of evidence: high risk of bias • Phase II trial • Open-label • Probably no ITT analysis
Moore 2011	• Design: RCT • Funding/CoI: 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; no CoI • Setting: single centre, Australia • Sample size: N=143 • Duration: recruitment period unclear; duration 12 weeks	• Eligibility criteria: Clinically stable ex-smokers with COPD on optimal medical treatment, having PaO2 >7.3 kPa at rest breathing room air and moderate to severe exertional dyspnoea • *A priori* patient characteristics: air vs. oxygen ○ Age: 72 vs. 72y ○ FEV1 % predicted: 47 vs. 47%	Cylinder air (N=75) vs. Cylinder oxygen (N=68)	Dyspnoea: mean (SD) • CRDQ: 4w 18.4 (5.8) vs. 19.7 (5.4), NS; 12w 18.4 (5.9) vs. 19.5 (6.0), NS Exercise tolerance: 6MWD • 4w: 359 (95.9) vs. 348 (99.9) • 12w: 357 (100) vs. 352 (114) Physical functioning: Not reported Quality of life: mean (SD) • CRDQ, total: 4w 87.6 (18.3) vs. 92.0 (19.9), NS; 12w 88.2 (20.5) vs. 89.6 (22.6), NS • Assessment of QOL utility index: 4w 0.52 (0.24) vs. 0.52 (0.26); 12w 0.57 (0.27) vs. 0.52 (0.27); NS	Level of evidence: high risk of bias • Concealed allocation • Blinded study • No ITT analysis (4 dropouts not included)
Ozalevli 2007	• Design: cross-over RCT	• Eligibility criteria: moderate-to-	6MWT in room air	Dyspnoea:	Level of evidence: high risk of

Study ID	Method	Patient characteristics	Interventions	Results	Critical appraisal of study quality
	• Funding/CoI: not reported • Setting: single university centre, Turkey • Sample size: N=28 • Duration: not reported	severe COPD, FEV1 % predicted <70%, exertional desaturation of at least 4%; clinically stable • *A priori* patient characteristics: intervention vs. control ○ Age: 68.9y ○ Male: N=22 ○ FEV1 % predicted: range 32-45%	conditions vs. 6MWT with supplemental oxygen	• Modified Borg scale: at the end of 6MWT 3.8 vs. 1.6, p=0.001 <u>Exercise tolerance</u>: • 6MW distance: 174.7 vs. 222.1m, p=0.001 <u>Physical functioning</u>: Not reported <u>Quality of life</u>: Not reported	bias • Pseudo-randomization: the patients were told that the two tests were identical and they chose the first test • Single blinded
Suzuki 2012	• Design: RCT • Funding/CoI: funded by the Grantsin-Aid for scientific research from the Japan Society of Acupuncture and Moxibustio; no CoI • Setting: multicentre study, Japan • Sample size: N=68 • Duration: recruitment period Jul 2006 – Mar 2009; duration 12 weeks	• Eligibility criteria: stage II-IV COPD, clinically stable with no history of infections or exacerbation of respiratory symptoms, no changes in medication within the 3 months preceding the study outset, and no signs of edema; stage II or higher dyspnea according to the MRC criteria; able to walk unassisted; no pulmonary rehabilitation in the previous 6 months • *A priori* patient characteristics: placebo vs. real acupuncture ○ Age: mean 72.5 vs. 72.7y ○ Male: 32 vs. 31 ○ FEV1 % predicted: 48.0 vs. 44.5 ○ Stage II: 13 vs. 6	Acupuncture once a week for 12 weeks (N=34) vs. Sham acupuncture (N=34)	<u>Dyspnoea</u>: • Borg scale after 6MWT: MD = -3.58; 95%CI -4.27 to -2.90 <u>Exercise tolerance</u>: • 6MWD: MD = 78.68 (95%CI 54.16 to 103.21) <u>Physical functioning</u>: Not reported <u>Quality of life</u>: • SGRQ, total: MD = -15.7 (95%CI -20.3 to -11.2)	Level of evidence: high risk of bias • Central randomization • Single blinded • No ITT analysis: 6 dropouts not included in analysis

Abbreviations: 6MWD: 6-minutes walking distance; 95%CI: 95% confidence interval; CCQ: Clinical COPD Questionnaire; CoI: conflicts of interest; COPD: chronic obstructive pulmonary disease; CRQ: Chronic Respiratory Disease Questionnaire; GARS: Groningen Activiteiten Restrictie Schaal; ITT: intention to treat; MA: meta-analysis; MD: mean difference; MRC: Medical Research Council; MRF: Maugeri Foundation Respiratory Failure; NIV: non-invasive ventilation; NRS: numeric rating scale; NS: non-significant; O2: oxygen; OR: odds ratio; PEP: positive expiratory pressure; QOL: quality of life; RCT: randomized controlled trial; RR: relative risk; SGRQ: St Georges Respiratory Questionnaire; SMD: standardized mean difference; SR: systematic review; SRI: Severe Respiratory Insufficiency; VAS: visual analogue scale; WMD: weighted mean difference

References

Bailey CD, Wagland R, Dabbour R, Caress A, Smith J, Molassiotis A. An integrative review of systematic reviews related to the management of breathlessness in respiratory illnesses. BMC pulmonary medicine. 2010;10(63).

Barton R, English A, Nabb S, Rigby AS, Johnson MJ. A randomised trial of high vs low intensity training in breathing techniques for breathless patients with malignant lung disease: a feasibility study. Lung Cancer. 2010;70(3):313-9.

Bausewein C, Booth S, Gysels M, Higginson I. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. Cochrane Database of Systematic Reviews. 2008;2(2):CD005623.

Bausewein C, Booth S, Gysels M, Kuhnbach R, Higginson IJ. Effectiveness of a hand-held fan for breathlessness: a randomised phase II trial. BMC Palliative Care. 2010;9:22.

Ben-Aharon I, Gafter-Gvili A, Leibovici L, Stemmer S.M. Interventions for alleviating cancer-related dyspnea: A systematic review and meta-analysis. Acta Oncol. 2012;51(8):996-1008.

Bradley JM, Lasserson T, Elborn S, Macmahon J, O'Neill B. A systematic review of randomized controlled trials examining the short-term benefit of ambulatory oxygen in COPD. Chest. 2007;131(1):278-85.

Chen H, Liang B-M, Xu Z-B, Tang Y-J, Wang K, Xiao J, et al. Long-term non-invasive positive pressure ventilation in severe stable chronic obstructive pulmonary disease: a meta-analysis. Chin Med J. 2011;124(23):4063-70.

Cranston JM, Crockett A, Currow D. Oxygen therapy for dyspnoea in adults. Cochrane Database of Systematic Reviews. 2008;3(3):CD004769.

DiSalvo WM, Joyce MM, Tyson LB, Culkin AE, Mackay K. Putting evidence into practice: evidence-based interventions for cancer-related dyspnea. Clin J Oncol Nurs. 2008;12(2):341-52.

Dreher M, Doncheva E, Schwoerer A, Walterspacher S, Sonntag F, Kabitz HJ, et al. Preserving oxygenation during walking in severe chronic obstructive pulmonary disease: noninvasive ventilation versus oxygen therapy. Respiration. 2009;78(2):154-60.

Duiverman ML, Wempe JB, Bladder G, Vonk JM, Zijlstra JG, Kerstjens HAM, et al. Two-year home-based nocturnal noninvasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients: a randomized controlled trial. Respiratory research. 2011;12(112).

Holland AE, Hill CJ, Jones AY, McDonald CF. Breathing exercises for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2012;10.

Hui D, Morgado M, Chisholm G, Withers L, Nguyen Q, Finch C, et al. High-flow oxygen and bilevel positive airway pressure for persistent dyspnea in patients with advanced cancer: a phase II randomized trial. J Pain Symptom Manage. 2013;46(4):463-73.

Kolodziej MA, Jensen L, Rowe B, Sin D. Systematic review of noninvasive positive pressure ventilation in severe stable COPD. Eur Respir J. 2007;30(2):293-306.

Lee EJ, Frazier SK. The efficacy of acupressure for symptom management: a systematic review. J Pain Symptom Manage. 2011;42(4):589-603.

Maggiore SM, Richard J-CM, Abroug F, Diehl JL, Antonelli M, Sauder P, et al. A multicenter, randomized trial of noninvasive ventilation with helium-oxygen mixture in exacerbations of chronic obstructive lung disease. Crit Care Med. 2010;38(1):145-51.

Norweg A, Collins EG. Evidence for cognitive-behavioral strategies improving dyspnea and related distress in COPD. International Journal of Copd. 2013;8:439-51.

Osadnik CR, McDonald CF, Miller BR, Hill CJ, Tarrant B, Steward R, et al. The effect of positive expiratory pressure (PEP) therapy on symptoms, quality of life and incidence of re-exacerbation in patients with acute exacerbations of chronic obstructive pulmonary disease: a multicentre, randomised controlled trial. Thorax. 2014;69(2):137-43.

Ozalevli S, Ozden A, Gocen Z, Cimrin AH. Comparison of six-minute walking tests conducted with and without supplemental oxygen in patients with chronic obstructive pulmonary disease and exercise-induced oxygen desaturation. Ann Saudi Med. 2007;27(2):94-100.

Pan L, Guo Y, Lio X, Yan J. Lack of efficacy of neuromuscular stimulation of the lower limbs in chronic obstructive pulmonary disease: a meta-analysis. Respirology 2014; 19: 22-29.

Struik FM, Lacasse Y, Goldstein R, Kerstjens HA, Wijkstra PJ. Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. Cochrane Database Syst Review 2013; 6: CD002878.Towler P, Molassiotis A, Brearley SG. What is the evidence for the use of acupuncture as an intervention for symptom management in cancer supportive and palliative care: an integrative overview of reviews. Support Care Cancer. 2013;21(10):2913-23.

Uronis H, McCrory DC, Samsa G, Currow D, Abernethy A. Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2011;6(6):CD006429.

Uronis HE, Currow DC, McCrory DC, Samsa GP, Abernethy AP. Oxygen for relief of dyspnoea in mildly- or non-hypoxaemic patients with cancer: a systematic review and meta-analysis. Br J Cancer. 2008;98(2):294-9.