Bijlage Evidence tabellen en GRADE profielen

Evidence tabellen en GRADE profielen behorende bij de oorspronkelijke onderzoeksvragen die in deze richtlijn via de GRADE-methodiek zijn uitgewerkt.

Onderzoeksvraag 1: Palliatieve zorg bij COPD

Wat is het effect van palliatieve zorg op symptomen en kwaliteit van leven van mensen met COPD?

Patiënten	Patiënten met COPD
Interventie	Palliatieve zorg
Comparator	Reguliere zorg
Outcome	Kritisch: dyspneu, kwaliteit van leven Belangrijk: vermoeidheid

Evidence tabellen

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Gomes 2013	• Design: systematic review • Funding: Cicely Saunders International, UK; Calouste Gulbenkian Foundation, Portugal; CoI: two authors were also authors of included studies • Search date: Nov 2012 • Databases: CENTRAL, EMBASE, MEDLINE, PaPas, EPOCs, CINAHL, PsycINFO, etc • Study designs: RCTs, CCTs, CBAs, ITSs • N included studies: N=23 (N=3 with COPD)	• Eligibility criteria: participants aged 18 years or older in receipt of a home palliative care service, their family caregivers, or both • In the three studies that included COPD patients, proportion of COPD patients was a third or less; no separate analyses were done for COPD in this systematic review	Home palliative care vs. usual care	CRITICAL OUTCOMES • Dyspnoea: no separate analysis for COPD • Quality of life: ○ Aiken 2006: SF-36 ▪ Physical functioning: slope 1.00 vs. -0,95, p<0,05 ▪ General health: slope 0,54 vs. -1.67, p<0,05 IMPORTANT OUTCOMES • Fatigue: no separate analysis for COPD	Level of evidence: high risk of bias • High-quality review • Review process in duplicate • Studies with COPD patients: Aiken 2006, Brumley 2007, Rabow 2004; no separate analyses for COPD in Brumley 2007 and Rabow 2004

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Mathews 2017	• Design: systematic review • Funding: None; CoI: authors report that there are no CoIs • Search date: 2015 - 2017 • Databases: MEDLINE, EMBASE, CINAHL, CENTRAL • Study designs: RCTs, qualitative research, SRs • N included studies: N=19 (3 RCTs)	• Eligibility criteria: adults (> 18 years) mainly with advanced/ severe COPD and palliative care needs	Palliative and end-of-life care processes or interventions: • Bove 2016: home-based psycho-educative intervention • Buckingham 2015: nurse-led home-based intervention • Shany 2017: home tele-monitoring	CRITICAL OUTCOMES • Dyspnoea: not reported • Quality of life: ○ Bove 2016: the intervention group had a higher post intervention CRQ-M score on average compared with the control group (p=0.016). The average differences between the groups were 0.58 points (95%CI 0.09-1.06) after 1 month and 0.67 points (95%CI 0.18-1.17) after 3 months IMPORTANT OUTCOMES • Fatigue: not reported	Level of evidence: high risk of bias • Limited to English language • Quality appraisal in duplicate, but unclear for selection process and data extraction • Included RCTs: Shany 2017, Bove 2016, Buckingham 2015; no measurable outcomes in Buckingham 2015; Shany 2017 did not study a palliative intervention, and thus is not further reported here
Ora 2019	• Design: systematic review • Funding: not reported; CoI: declared having no CoI • Search date: Jan 2008 - Dec 2018 • Databases: ProQuest Central, MEDLINE, PubMed Central, CINAHL, Scopus, PsychInfo and Google Scholar • Study designs: mixed-study types • N included studies: N=6, of which 4 RCTs	• Eligibility criteria: patients with COPD receiving palliative care	Nurse-led palliative care model interventions	CRITICAL OUTCOMES • Dyspnoea: not reported • Quality of life: ○ Weber 2017 (abstract): both groups demonstrated a significant improvement in QOL (SF-36 and CAT) 3 and 6 months after inclusion, but there was no group effect and no effect overtime after 6 months IMPORTANT OUTCOMES • Fatigue: not reported	Level of evidence: high risk of bias • Limited to English language • Selection process in duplicate, data extraction and quality appraisal not clear • Included RCTs: Weber 2017 (abstract), Buckingham 2015, Houben 2018 (protocol), Sinclair 2017; no measurable outcomes in Buckingham 2015; no separate results for COPD in Sinclair 2017
Singer 2016	• Design: systematic review • Funding: supported by a range of grants; CoI: authors report having no	• Eligibility criteria: adults of 18 years and older with advanced illness including COPD patients	Interventions for palliative and end-of-life care	CRITICAL OUTCOMES • Dyspnoea: not reported • Quality of life: ○ Aiken 2006: SF-36	Level of evidence: high risk of bias • Limited to English language

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	competing financial interests • Search date: Jan 2001 - Aug 2015 • Databases: MEDLINE, EMBASE, PsycINFO, Web of Science, and Cochrane Database of Systematic Reviews • Study designs: RCTs • N included studies: N=124 (n=19 with COPD)	(most studies also included patients with cancer or CHF)		▪ Physical functioning: slope 1.00 vs. -0.95, p<0.05 ▪ General health: slope 0.54 vs. -1.67, p<0.05 ○ Au 2012: see below ○ Egan 2002: SGRQ at 1 mo (median change) ▪ Symptoms: -17.5 vs. -9.3, p=0.384 ▪ Activities: 0 vs. 0.4, p=0.727 ▪ Impacts: -0.2 vs. -0.9, p=0.849 ▪ Total: -1.6 vs. -1.5, p=0.621 IMPORTANT OUTCOMES • Fatigue: not reported	• Selection process and data extraction in duplicate, quality appraisal not • Relevant studies (with separate results for COPD): Aiken 2006, Au 2012, Egan 2002, Rea 2004; Rea 2004 did not study a palliative intervention, and thus is not further reported here

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Duenk 2017	• Design: cluster-RCT • Funding: funded by the Netherlands Organization for Health Research and Development ZonMw; CoI: authors report having no CoI • Setting: 6 Hospitals, the Netherlands • Sample size: N=228 • Duration: Jan 2014 - Jan 2015, 1 year follow-up	• Eligibility criteria: patients with COPD, 18 years or older, who had a hospital admission for an AECOPD • Exclusion: not speaking Dutch, with severe cognitive disorders or treated at that moment with special palliative care • *A priori* patient characteristics: ○ Mean age: 68.5y ○ Male: 48 % ○ Residence: home, independent of home care: 63%; home, dependent of home care: 32.5%, residential home: 1.3% ○ Predicted FEV_1: 42.5% ○ Vital capacity: 2.6 L	Proactive palliative care with monthly meetings with a specialized palliative care team + usual care (N=90) vs. Usual care alone (N=138)	CRITICAL OUTCOMES • Dyspnoea: not reported • Quality of life: ○ SGRQ total: ▪ Change from baseline (3 mo): MD -0.79 (95%CI -4.61 to 3.34, p=0.70) ▪ Change from baseline (6 mo): MD -2.20 (95%CI -6.63 to 2.22, p=0.36) ▪ Change from baseline (9 mo): MD -4.26 (95%CI -8.55 to 0.03, p=0.07) ▪ Change from baseline (12 mo): MD -1.70 (95%CI -6.71 to 3.32, p=0.54) ○ McGill total (3 mo): MD 0.26 (−0.30 to 0.83, p=0.43) IMPORTANT OUTCOMES • Fatigue: not reported	Level of evidence: high risk of bias • Cluster trial • No randomisation: treatment allocation based on availability of palliative team • Only patients were blinded • 29% drop out after 3 months

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		○ GOLD-stage: 0: 10, I=7, II 51, III= 87, IV=63 ○ SGRQ total-score 68.12 ○ McGill total score 5.16 ○ HADS total score 16.87			
Janssens 2019	• Design: RCT • Funding: financed by Swiss National Foundation for Research; CoI: authors report having no CoI • Setting: Geneva university hospital, Switzerland • Sample size: N=49 • Duration: 12 months	• Eligibility criteria: Patients with severe COPD (GOLD stage III and IV) and long-term oxygen therapy, home non-invasive ventilation, previous hospital admissions for acute exacerbations • *A priori* patient characteristics: ○ Mean age: 71 years ○ Male: 47% ○ FEV_1: 37% ○ COPD assessment score >10: 88% ○ On long-term oxygen therapy or home ventilation: 69% ○ Past smoker: 90% ○ Active smokers: 33% ○ BMI: 24.8 kg/m2	Intervention: home early palliative care + usual care (N=26); monthly home visits by nurse for 12 months, focusing on symptom assessment and management, nutrition, understanding of illness and coping, anticipation and decision-making, support of relatives, social-spiritual needs, coordination between different health providers, and alternative approaches vs. Control: usual care (N=23)	CRITICAL OUTCOMES • Dyspnoea: only measured in intervention group • Quality of life: none of the SF-36 items differed significantly between groups at inclusion or during follow-up (detailed data only provided in figures in supplementary data) IMPORTANT OUTCOMES • Fatigue: only measured in intervention group	Level of evidence: high risk of bias • Randomization with 1:1 ratio without stratification and with randomized block sizes 4-6 • Sealed envelopes: not opaque? But by co-investigator not involved • Blinding of patients and clinicians not possible • Data were collected by research nurse independent from palliative care team • Intention-to-treat analysis
Scheerens 2019	• Design: RCT • Funding: grant from Strategisch Basis Onderzoek / Agentschap Innoveren en Ondernemen; CoI: authors declare no CoI	• Eligibility criteria: Patients with end-stage COPD having GOLD III or IV, being dependent on oxygen with MRC scale dyspnoea 4, and non-invasive ventilation the past year	Early integrated palliative home care (N=20) vs. Standard care (N=19)	CRITICAL OUTCOMES • Dyspnoea: not reported • Quality of life: ○ SF-36 Physical (95%CI): ▪ Week 6: 28.7 (25.2-32.3) vs. 24.3 (20.4-28.1)	Level of evidence: high risk of bias • Randomisation: permuted block method (block size of 4), stratified according to recruiting hospital

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Setting: Ghent University hospital, Belgium • Sample size: N=39 • Duration: 6 months	• Exclusion: patients in last days of life, with cognitive impairments, lung cancer diagnosis, active cancer or no longer living at home • *A priori* patient characteristics: ○ Mean age:67 years ○ Male: 56% ○ Limit for heavy physical activities: 28% ○ Fully disabled: 13% ○ Years diagnosed with COPD: 9.8 ○ GOLD IV: 87%		▪ Week 12: 28.3 (24.8-31.8) vs. 23.4 (19.6-27.2) ▪ Week 18: 27.1 (23.4-30.8) vs. 23.7 (20.0-27.5) ▪ Week 24: 23.6 (19.8-27.3) vs. 22.9 (19.0-26.8) ▪ Interaction effects: p=0.12 ○ SF-36 Mental (95%CI): ▪ Week 6: 38.2 (32.8-43.6) vs. 38.1 (32.5-43.8) ▪ Week 12: 40.7 (35.3-46.0) vs. 36.4 (30.9-42.0) ▪ Week 18: 38.4 (32.9-43.9) vs. 38.4 (32.8-43.9) ▪ Week 24: 35.6 (30.0-41.1) vs. 37.4 (31.7-43.2) ▪ Interaction effects: p=0.16 IMPORTANT OUTCOMES • Fatigue: not reported	• Computer-generated sequences • Only the research assistant obtained the allocation sequence, patient study numbers, and the corresponding allocation from the statistician for enrollment • No blinding • Only 64% completed the trial

Abbreviations: 95%CI: 95% confidence interval; ACP: advance care planning; AECOPD: acute exacerbation of COPD; BMI: body mass index; CoI: conflicts of interest; COPD: chronic obstructive pulmonary disease; CRQ-M: chronic respiratory questionnaire – mastery; FEV_1: forced expiratory volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HADS: Hospital Anxiety and Depression Scale; ICU: intensive care unit; IRR: incidence rate ratio; MD: mean difference; MRC: Medical Research Council; QOC: quality of communication; QOL: quality of life; RCT: randomized controlled trial; SD: standard deviation; SF-36: short form 36; SGRQ: St. George Resipratory Questionnaire.

GRADE profielen

Home-based nurse-led case management

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95%CI)	Absolute		
Dyspnoea												
0	No evidence from RCTs											

Quality of life: SF-36												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	100	90	-	Physical functioning: slope 1.00 vs. -0.95, p<0.05 General health: slope 0.54 vs. -1.67, p<0.05	LOW	CRITICAL
Fatigue												
0	No evidence from RCTs											IMPORTANT

[1] High risk of bias: possible issues with blinding; no ITT analysis.

[2] No relative effect reported, no information on 95%CI.

Nurse-led case management

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**	**Relative (95%CI)**	**Absolute**		
Dyspnoea												
0	No evidence from RCTs											
Quality of life: SGRQ (median change)												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	27	26	-	Symptoms: -17.5 vs. -9.3, p=0.384 Activities: 0 vs. 0.4, p=0.727	LOW	CRITICAL

										Impacts: -0.2 vs. -0.9, p=0.849 Total: -1.6 vs. -1.5, p=0.621		
Fatigue												
0	No evidence from RCTs											IMPORTANT

[1] High risk of bias: possible issues with blinding; no ITT analysis.

[2] Insufficient data to estimate precision.

Home-based psycoeducative intervention

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**	**Relative (95%CI)**	**Absolute**		
Dyspnoea												
0	No evidence from RCTs											
Quality of life: CRQ-M												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	30	27	Difference 3 mo post-intervention: 0.67 (0.18-1.17) p=0.016	-	LOW	CRITICAL
Fatigue												
0	No evidence from RCTs											IMPORTANT

[1] High risk of bias: possible issues with blinding; no ITT analysis.

[2] SMD = 0.70 (95%CI 0.16-1.24): CI includes 0.5.

Proactive palliative care

Quality assessment	**No of patients**	**Effect**	**Quality**	**Importance**

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95%CI)	Absolute		
Dyspnoea												
0	No evidence from RCTs											
Quality of life: SGRQ (change from baseline)												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision[2]	None	62	88	3 months: MD -0.79 (-4.61 to 3.34, p=0.70)	-	LOW	CRITICAL
					Serious[3]		55	70	6 months: MD -2.20 (-6.63 to 2.22, p=0.36)		VERY LOW	
					Serious[4]		53	69	9 months: MD -4.26 (-8.55 to 0.03, p=0.07)		VERY LOW	
					Serious[5]		45	63	12 months: MD -1.70 (-6.71 to 3.32, p=0.54)		VERY LOW	
Fatigue												
0	No evidence from RCTs											IMPORTANT

[1] High risk of bias: no randomization; possible issues with blinding; no ITT analysis.

[2] SMD = -0.17 (95%CI -0.49 to 0.16).

[3] SMD = -0.24 (95%CI -0.59 to 0.12); CI includes -0.5.

[4] SMD = -0.36 (95%CI -0.72 to 0.00); CI includes -0.5.

[5] SMD = -0.19 (95%CI -0.57 to 0.20); CI includes -0.5.

"Early" home-based nurse-led palliative care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**	**Relative (95%CI)**	**Absolute**		

Dyspnoea												
0	No evidence from RCTs											
Quality of life: SF-36												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	26	23	"None of the SF-36 items differed significantly between groups at inclusion or during follow-up"	-	VERY LOW	CRITICAL
Fatigue												
0	No evidence from RCTs											IMPORTANT

[1] High risk of bias: no blinding.

[2] Insufficient data to estimate precision (only reported in graphs in supplementary file).

"Early" home-based palliative care

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**	**Relative (95%CI)**	**Absolute**		
Dyspnoea												
0	No evidence from RCTs											
Quality of life: SF-36 – physical												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	16	13	6w: 28.7 vs. 24.3	-	LOW	CRITICAL
					Serious[3]		17	14	12w: 28.3 vs. 23.4		LOW	
					Serious[4]		14	14	18w: 27.1 vs. 23.7		LOW	
					Very serious[5]		13	12	24w: 23.6 vs. 22.9		VERY LOW	

Quality of life: SF-36 – mental												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[6]	None	16	13	6w: 38.2 vs. 38.1	-	VERY LOW	CRITICAL
					Serious[7]		17	14	12w: 40.7 vs. 36.4		LOW	
					Very serious[8]		14	14	18w: 38.4 vs. 38.4		VERY LOW	
					Very serious[9]		13	12	24w: 35.6 vs. 37.4		VERY LOW	
Fatigue												
0	No evidence from RCTs											IMPORTANT

[1] High risk of bias: no blinding; no ITT analysis.

[2] SMD = 0.64 (95%CI -0.11 to 1.39); CI includes 0.5.

[3] SMD = 0.70 (95%CI -0.03 to 1.43); CI includes 0.5.

[4] SMD = 0.52 (95%CI -0.24 to 1.27); CI includes 0.5.

[5] SMD = 0.11 (95%CI -0.68 to 0.89); CI includes 0.5 at both sides.

[6] SMD = 0.04 (95%CI -0.69 to 0.77); CI includes 0.5 at both sides.

[7] SMD = 0.41 (95%CI -0.30 to 1.13); CI includes 0.5.

[8] SMD = 0.00 (95%CI -0.74 to 0.74); CI includes 0.5 at both sides.

[9] SMD = -0.19 (95%CI -0.98 to 0.60); CI includes 0.5 at both sides.

Referenties

1. Duenk RG, Verhagen C, Bronkhorst EM, van Mierlo P, Broeders M, Collard SM, et al. Proactive palliative care for patients with COPD (PROLONG): a pragmatic cluster controlled trial. Int J Chron Obstruct Pulmon Dis. 2017;12:2795-806.
2. Gomes B, Calanzani N, Curiale V, McCrone P, Higginson IJ. Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. Cochrane Database Syst Rev. 2013;2016(3).
3. Janssens JP, Weber C, Herrmann FR, Cantero C, Pessina A, Matis C, et al. Can Early Introduction of Palliative Care Limit Intensive Care, Emergency and Hospital Admissions in Patients with Severe Chronic Obstructive Pulmonary Disease? A Pilot Randomized Study. Respiration. 2019;97(5):406-15.
4. Mathews G, Johnston B. Palliative and end-of-life care for adults with advanced chronic obstructive pulmonary disease: a rapid review focusing on patient and family caregiver perspectives. Curr. 2017;11(4):315-27.
5. Ora L, Mannix J, Morgan L, Wilkes L. Nurse-led integration of palliative care for chronic obstructive pulmonary disease: An integrative literature review. J Clin Nurs. 2019;28(21-22):3725-33.

6. Scheerens C, Pype P, Van Cauwenberg J, Vanbutsele G, Eecloo K, Derom E, et al. Early-Integrated Palliative home care and standard care for end-stage COPD (EPIC): A Phase II pilot RCT testing feasibility, acceptability and effectiveness. J Pain Symptom Manage. 2019;09:09.
7. Singer AE, Goebel JR, Kim YS, Dy SM, Ahluwalia SC, Clifford M, et al. Populations and Interventions for Palliative and End-of-Life Care: A Systematic Review. J Palliat Med. 2016;19(9):995-1008.

Onderzoeksvraag 2: Proactieve zorgplanning
Wat is het effect van proactieve zorgplanning (advance care planning, ACP) bij patiënten met COPD en hun naasten?

Patiënten	Patiënten met COPD
Interventie	ACP
Comparator	Geen ACP, reguliere zorg
Outcome	Kritisch: levensverlengende maatregelen, tevredenheid van patiënten en verzorgers Belangrijk: ziekenhuisopnames, plaats van zorg, plaats van overlijden

Evidence tabellen
Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Jabbarian 2018	• Design: systematic review • Funding: Research program via European Comission; CoI: not reported • Search date: June 2015 • Databases: Embase, MEDLINE, Web of Science, Scopus, CINAHL EBSCO, PsycINFO, Cochrane, PubMed, LILACS, SciELO, ProQuest and Google Scholar • Study designs: Quantitative and qualitative designs • N included studies: N=21 (n=13 with COPD)	• Eligibility criteria: Adults with chronic respiratory diseases	ACP	• One RCT included: Au 2012 Discussed in detail below	Level of evidence: high risk of bias • Limited to English language • Review process in duplicate
Meehan 2019	• Design: systematic review; scoping review	• Eligibility criteria: Individuals with COPD	ACP	• Four RCTs included: o Duenk 2017: excluded from our search, ACP part of larger intervention	Level of evidence: high risk of bias

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Funding: supported by grant from GlaxoSmithKline; CoI: report having no CoI • Search date: January 2009 until May 2019 • Databases: PubMed, CINAHL Plus, EBSCO, and The Cochrane Library • Study designs: Primary research studies of any design • N included studies: N=28			○ Houben 2019: discussed in detail below ○ Sinclair 2017: no separate results for COPD ○ Thoonsen 2015: no separate results for COPD	• Limited to English language • Selection process in duplicate, data extraction not • No quality appraisal done because of scoping review design
Ora 2019	• Design: systematic review; mixed-studies integrative review • Funding: not reported; CoI: report having no CoI • Search date: January 2008 until December 2018 • Databases: ProQuest Central, MEDLINE, PubMed Central, CINAHL, Scopus, PsychInfo and Google Scholar • Study designs: RCTs, descriptive paper and literature review • N included studies: N=6	• Eligibility criteria: Patients with COPD	Nurse-led interventions with integrated palliative care, including advance care planning. Two types: specialist palliative care nurses; experienced respiratory nurses having received palliative care training	• Four RCTs included: ○ Weber 2017: abstract ○ Buckingham 2015: no ACP ○ Houben 2014 & 2018: protocol ○ Sinclair 2017: no separate results for COPD	Level of evidence: high risk of bias • Limited to English language • Selection process in duplicate, data extraction and quality appraisal not clear

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Janssens 2019	• Design: RCT • Funding: financed by Swiss National Foundation for Research; CoI: authors report having no CoI • Setting: Geneva university hospital, Switzerland • Sample size: N=49 • Duration: 12 months	• Eligibility criteria: Patients with severe COPD (GOLD stage III and IV) and long-term oxygen therapy, home non-invasive ventilation, previous hospital admissions for acute exacerbations • *A priori* patient characteristics: o Mean age: 71 years o Male: 47% o FEV_1: 37% o COPD assessment score >10: 88% o On long-term oxygen therapy or home ventilation: 69% o Past smoker: 90% o Active smokers: 33% o BMI: 24.8 kg/m2	Intervention: home early palliative care + usual care (N=26); monthly home visits by nurse for 12 months, focusing on symptom assessment and management, nutrition, understanding of illness and coping, anticipation and decision-making, support of relatives, social-spiritual needs, coordination between different health providers, and alternative approaches vs. Control: usual care (N=23)	CRITICAL OUTCOMES • Life-sustaining treatments (resuscitation, ventilation, ICU admission): o Admissions to ICU for respiratory failure: IRR 4.42 (0.49-20.92; p=0.163) • Satisfaction of patients and carers: o QOL: none of the SF-36 items differed significantly between groups at inclusion or during follow-up (detailed data only provided in figures in supplementary data) IMPORTANT OUTCOMES • Hospital admissions: o Admissions to emergency ward: IRR 2.05 (95%CI 1.11-3.94; p=0.014) o Hospital admissions for respiratory failure: IRR 1.87 (1.04-3.48; p:0.026) o Hospital admissions for other reasons: IRR 1.01 (0.32-3.28; p=0.988) • Place of care (hospital, hospice, home…): not reported • Place of death: not reported	Level of evidence: high risk of bias • Randomization with 1:1 ratio without stratification and with randomized block sizes 4-6 • Sealed envelopes: not opaque? But by co-investigator not involved • Blinding of patients and clinicians not possible • Data were collected by research nurse independent from palliative care team • Intention-to-treat analysis

Abbreviations: 95%CI: 95% confidence interval; ACP: advance care planning; BMI: body mass index; CoI: conflicts of interest; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HADS-A: Hospital Anxiety and Depression Scale – anxiety; ICU: intensive care unit; IRR: incidence rate ratio; MD: mean difference; QOC: quality of communication; QOL: quality of life; RCT: randomized controlled trial; SD: standard deviation.

GRADE profielen

ACP vs. no ACP

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95%CI)	Absolute		
Admissions to ICU for respiratory failure												

1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	26	23	IRR = 4.42 (0.49-20.92) p=0.163	-	VERY LOW	CRITICAL
Satisfaction of patients and carers: rate of discussions about end-of-life care												
1	RCT	Very serious[4]	No serious inconsistency	No serious indirectness	Very serious[5]	None	194	182	-	Absolute difference of 18.6% (p<0.001)	VERY LOW	CRITICAL
Satisfaction of patients and carers: quality of communication score												
2	RCT	Very serious[4]	No serious inconsistency	No serious indirectness	Very serious[5]	None	194	182	Adjusted difference in change from baseline = 5.74 p=0.03	-	VERY LOW	CRITICAL
	RCT	Very serious[6]	No serious inconsistency	No serious indirectness	No serious imprecision	None	71	63	Adjusted MD = 2.01 (1.07-2.95) p<0.001	-	LOW	CRITICAL
Satisfaction of patients and carers: quality of death and dying score												
1	RCT	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	?	?	-	Mean (SD): 80.01 (8.57) vs. 74.71 (11.51) p=0.17		CRITICAL
Hospital admissions: hospital admissions for respiratory failure												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	26	23	IRR = 1.87 (1.04-3.48) p=0.026	-	LOW	IMPORTANT
Hospital admissions: hospital admissions for other reasons												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	26	23	IRR = 1.01 (0.32-3.28) p=0.988	-	VERY LOW	IMPORTANT
Hospital admissions: admissions to emergency ward												

1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	26	23	IRR = 2.05 (1.11-3.94) p=0.014	-	LOW	IMPORTANT
Place of care (hospital, hospice, home…)												
0	No evidence											IMPORTANT
Place of death												
0	No evidence											IMPORTANT

[1] High risk of bias: possible issues with allocation concealment, no blinding of patients and clinicians.

[2] Very large confidence interval in both directions.

[3] Confidence includes upper 25% limit.

[4] High risk of bias: unclear allocation concealment, no blinding of patients and clinicians, selective outcome reporting for rate of discussions (no 95%CI reported).

[5] Insufficient data to evaluate imprecision.

[6] High risk of bias: unclear randomization, clinicians aware of intervention, no intention-to-treat analysis.

Referenties

1. Jabbarian LJ, Zwakman M, van der Heide A, Kars MC, Janssen DJA, van Delden JJ, et al. Advance care planning for patients with chronic respiratory diseases: a systematic review of preferences and practices. Thorax. 2018;73(3):222-30.
2. Janssens J-P, Weber C, Herrmann François R, Cantero C, Pessina A, Matis C, et al. Can Early Introduction of Palliative Care Limit Intensive Care, Emergency and Hospital Admissions in Patients with Severe Chronic Obstructive Pulmonary Disease? A Pilot Randomized Study. Respiration. 2019;97(5):406-15.
3. Meehan E, Foley T, Kelly MC, Burgess Kelleher A, Sweeney C, Hally RM, et al. Advance care planning for individuals with chronic obstructive pulmonary disease: a scoping review of the literature. J Pain Symptom Manage. 2019;11:11.
4. Ora L, Mannix J, Morgan L, Wilkes L. Nurse-led integration of palliative care for chronic obstructive pulmonary disease: An integrative literature review. J Clin Nurs. 2019;28(21-22):3725-33.

Onderzoeksvraag 3: Psychosociale zorg
Wat is het effect van (niet-)medicamenteuze behandeling op angst bij mensen met COPD?

Patiënten Patiënten met COPD
Interventie Medicamenteuze en niet-medicamenteuze behandeling van angst
Comparator Andere interventie, placebo, geen behandeling
Outcome Kritisch: angst

Evidence tabellen
Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Baraniak 2011	• Design: systematic review • Funding: not reported; CoI: not reported • Search date: Sep 2009 • Databases: Cochrane Library and MEDLINE, PsycARTICLES, PsycINFO, Web of Science • Study designs: comparative studies • N included studies: N=9, of which 6 RCTs	• Eligibility criteria: patients with a confirmed diagnosis of COPD without co-morbidities of asthma or other significant health problems impacting psychological intervention • Four studies included patients with moderate to severe COPD and one study included patients with mild to severe COPD; the remaining four studies confirmed diagnosis with spirometry, but did not report disease severity • Mean age: from 66-71 years	Psychologically based interventions	CRITICAL OUTCOMES • Anxiety: meta-analysis based on pre- and post-intervention anxiety scores (N=222) had a combined effect size of r = -0.273 (95%CI -0.419 to -0.141; p<0.00004) (8 studies)	Level of evidence: high risk of bias • Review process partially in duplicate (only data extraction 50%) • Limited to English studies • Combination of different study designs in meta-analysis
Coventry 2013	• Design: systematic review • Funding: funded by NIHR; CoI: authors declare not having CoI • Search date: Apr 2012 • Databases: CENTRAL, Medline, Embase, PsychINFO, CINAHL, ISI Web of Science, Scopus	• Eligibility criteria: Individuals with confirmed COPD • Median age of 66.3 years; • Most patients had moderate or severe COPD; only one study with mild to moderate COPD patients	Single or multiple component interventions that include psychological and/or lifestyle components	CRITICAL OUTCOMES • Anxiety: o Overall SMD: -0.24 (95%CI -0.39 to -0.09) o Multi-component exercise training: SMD -0.45 (95%CI -0.71 to -0.18) o CBT: SMD -0.12 (95%CI -0.34 to 0.11) o Self-management education: SMD -0.01 (95%CI -0.25 to 0.24) o Relaxation: SMD -0.22 (95%CI -0.65 to 0.21)	Level of evidence: high risk of bias • Only 4 studies with anxiety at baseline (Bucknall 2012, de Godoy 2003, Hynninen 2010, Kunik 2008), anxiety scores were reported in 26 studies • Review process in duplicate

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Study designs: RCTs • N included studies: N=32			○ Subgroup of samples with anxiety: SMD -0.21 (95%CI -0.36 to -0.03)	• No language restriction
Gordon 2019	• Design: systematic review • Funding: one author received Lung Foundation Australia/Boehringer-Ingelheim COPD Research Fellowship; CoI: authors declared no financial/ nonfinancial disclosures • Search date: February 2018 • Databases: MEDLINE (Ovid), CINAHL, PEDro, the Cochrane Library • Study designs: RCTs • N included studies: N=11	• Eligibility criteria: patients with COPD	Pulmonary rehabilitation	CRITICAL OUTCOMES • Anxiety: pooled SMD = -0.53 (95%CI -0.82 to -0.23); I^2 63% ○ program duration (< 8 vs. > 8 weeks) showed no significant difference (p=0.66)	Level of evidence: high risk of bias • 11 studies included, of which 10 were pooled in a meta-analysis • Review process in duplicate • Limited to English studies
Harrison 2016	• Design: systematic review • Funding: funded by the Ontario Respiratory Care Society; CoI: declared 'none' • Search date: March 2015 • Databases: PubMed, CINAHL, PsychINFO, EMBASE and MEDLINE • Study designs: RCTs; studies applying quantitative methodologies • N included studies: N=4	• Eligibility criteria: adults (age > 18 years) with a respiratory diagnosis who are limited by symptoms of dyspnoea • 2 out of 4 studies involved individuals with COPD	Mindfulness-Based Stress Reduction or Mindful Cognitive Behavioral Therapy	CRITICAL OUTCOMES • Anxiety: ○ Chan 2015: anxiety improved in the intervention group compared to the control group, but no significant difference (no quantitative data reported)	Level of evidence: high risk of bias • 4 studies included, of which 2 RCTs about COPD (Mularski 2009, Chan 2015); only one study reported anxiety • Review process in duplicate • Limited to English studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Jolly 2018	• Design: systematic review • Funding: NIHR-support; CoI: declared no CoI • Search date: September 2017 • Databases: MEDLINE, EMBASE, CENTRAL, etc • Study designs: RCTs • N included studies: N=12	• Eligibility criteria: Studies of adult patients with predominantly (>90%) COPD from primary care ○ Mean age: 61-73 years ○ Male: 48% ○ FEV_1: 51 – 66%	Community-based self-management	CRITICAL OUTCOMES • Anxiety: ○ HADS anxiety was not significantly different between intervention and controls: MD = -0.35 (95%CI -0.91 to 0.21; I^2 37.1) (4 studies, N=676)	Level of evidence: high risk of bias • 4 studies reported on anxiety (Howard 2014, Mitchell 2014, Taylor 2012, Walters 2014) • Review process in duplicate • No language restriction
Lee 2015	• Design: systematic review • Funding: no funding received; CoI: authors reported no CoI • Search date: June 2014 • Databases: MEDLINE, CINAHL, Embase, PubMed, CAIRSS, etc • Study designs: RTCs, cohort studies • N included studies: N=13, of which 5 RCTs	• Eligibility criteria: Patients with COPD	Distractive auditory stimulus (DAS)	CRITICAL OUTCOMES • Anxiety: ○ Bauldoff 2002: adding DAS to exercise training for a 2-month duration had no effect on anxiety (no numbers reported) ○ Singh 2009: general anxiety decreased with DAS compared with relaxation techniques (p=0.003)	Level of evidence: high risk of bias • Included RCTs that reported anxiety: Bauldoff 2002, Singh 2009 • Review process in duplicate • Unclear if language restriction • GRADE applied in wrong way
Ma 2019	• Design: systematic review • Funding: no funding received; CoI: reported as 'none' • Search date: July 2019 • Databases: PubMed, Cochrane library, EMBASE, Web of Science and China National Knowledge Infrastructure databases • Study designs: RCT • N included studies: N=16	• Eligibility criteria: individuals with an objective diagnosis of COPD according to pulmonary function or the GOLD criteria ○ Male: 63% ○ Age >=40 years ○ Duration/follow-up: 3 weeks – 1year	Cognitive behavioural therapy (CBT)	CRITICAL OUTCOMES • Anxiety: ○ SMD = -0.23 (95%CI -0.42 to -0.04; p=0.02) (12 studies)	Level of evidence: high risk of bias • Review process in duplicate • Limited to English and Chinese language

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Simon 2016	• Design: systematic review • Funding: The Federal Ministry of Education and Research Germany; CoI: none known • Search date: August 2016 • Databases: CENTRAL, MEDLINE, EMBASE • Study designs: RCTs, CCTs • N included studies: N=8 (5 with COPD patients)	• Eligibility criteria: Adult participants described as suffering from either breathless-ness, dyspnoea, shortness of breath, difficult breathing, or laboured breathing due to advanced malignant and non-malignant diseases	Benzodiazepines	CRITICAL OUTCOMES • Anxiety: ○ Benzodiazepines did not reduce anxiety, either as a change from baseline or compared to the control group after treatment (based on studies including COPD and cancer patients; no numeric data)	Level of evidence: high risk of bias • Only 1 RCT reported on anxiety in COPD patients: Woodcock 1981 • Review process in duplicate • No language restriction
Usmani 2011	• Design: systematic review • Funding: Australasian Cochrane Airways Group Network, Australia; CoI: None known • Search date: June 2011 • Databases: CCDANCTR, MEDLINE, EMBASE, PsychInfo, CENTRAL • Study designs: RCTs • N included studies: N=4	• Eligibility criteria: patients (age > 40 years) with clinically significant COPD and a recognised anxiety disorder or anxiety symptoms	Pharmacological interventions	CRITICAL OUTCOMES • Anxiety: ○ SSRI vs. placebo: MD -2.37 (95%CI -5.44 to 0.70) (2 studies, N=21) ○ TCA vs. placebo: MD 0.30 (95%CI -3.42 to 4.02) (1 study) ○ Azapirones vs. placebo: MD 3.50 (95%CI -9.04 to 16.04) (1 study)	Level of evidence: high risk of bias • Review process in duplicate • No language restriction
Usmani 2017	• Design: systematic review • Funding: NIHR; CoI: grants from Cochrane, Thoraic Society Australia, grants from multiple organisations, a variety of commercial companies, etc • Search date: August 2015 • Databases: CCMD, CAG, MEDLINE, EMBASE,	• Eligibility criteria: patients with COPD over 40 years and coexisting anxiety disorder	Psychological therapies	CRITICAL OUTCOMES • Anxiety: ○ MD -4.41 (95%CI -8.28 to -0.53; p=0.03) on Beck Anxiety Inventory (3 studies, N=319)	Level of evidence: high risk of bias • Review process in duplicate • No language restriction

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	PsycInfo, The Cochrane Library • Study designs: RCTs • N included studies: N=3				

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Mhaske 2018	• Design: RCT • Funding: not reported; CoI: declared having no CoI • Setting: Krishna Hospital, Karad, India • Sample size: N=56 • Duration: not reported	• Eligibility criteria: Patients with moderate COPD, FEV/forced vital capacity <70% and FEV_1<80%, HADS-score 8-12, being able to communicate and listen • Exclusion: receiving tricyclic antidepressants or other antipsychotic, having cardiovascular disease, uncontrolled hypertension, or evidence of evidence of neurological or musculoskeletal condition • *A priori* patient characteristics: ○ Mean age: 45 years ○ Men: 69%	Visual imagery technique (VIT; N=28) vs. Progressive relaxation technique (PRT; N=28)	CRITICAL OUTCOMES • Anxiety: ○ HADS post-treatment: 3.63 vs. 9.13, t=9.220, p<0.0001 ○ DASS21 post-treatment: 3.09 vs. 5.08, t=5.115, p<0.0001	Level of evidence: high risk of bias • Unclear randomization and allocation method • Unclear blinding (but unlikely) • Higher DASS21-scores pre-treatment in VIT-group • 11 lost-to-follow-up, excluded from analysis
Usmani 2018	• Design: RCT • Funding: The Queen Elizabeth Hospital, Adelaide, SA, Australia; CoI: authors report no CoI • Setting: The Queen Elizabeth Hospital, Australia	• Eligibility criteria: Patients with COPD older than 40 years and clinically significant anxiety (>15 score on Beck Anxiety Inventory BAI) • Exclusion: current or recent exacerbation of COPD, terminal cancer, any other concurrent	Daily paroxetine 20 mg (N=18) vs. Placebo (N=20)	CRITICAL OUTCOMES • Anxiety: ○ BAI: change from baseline -11.9 vs. -3.16 (p=0.007)	Level of evidence: high risk of bias • Double-blind study • Only 22 patients completed the study: no ITT-analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Sample size: N=38 • Duration: 4 months	significant psychological disease; recent use of monoamine oxidase inhibitor; pregnancy or lactation, sever liver, kidney, cardiovascular or locomotor disease, or uncontrolled epilepsy • *A priori* patient characteristics: ○ Mean age: 69 years ○ Male: 53 % ○ Current smokers: 29%			

Abbreviations: 95%CI: 95% confidence interval; BMI: body mass index; CBT: cognitive behavioral treatment; CoI: conflicts of interest; COPD: chronic obstructive pulmonary disease; CRQ-M: chronic respiratory questionnaire – mastery; DAS: distractive auditory stimulus; DASS21: Depression Anxiety Stress Scale; FEV_1: forced expiratory volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HADS: Hospital Anxiety and Depression Scale; ICU: intensive care unit; IRR: incidence rate ratio; MD: mean difference; MRC: Medical Research Council; QOC: quality of communication; QOL: quality of life; RCT: randomized controlled trial; SD: standard deviation; SF-36: short form 36; SMD: standardized mean difference; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressants.

GRADE profielen

Psychological therapies

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Psychological therapy**	**Control**	**Relative (95%CI)**	**Absolute**		
Anxiety												
9	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	?	?	SMD = -0.21 (-0.36 to -0.06)	-	MODERATE	CRITICAL
3	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	157	162	MD = -4.41 (-8.28 to -0.53)	-	MODERATE	CRITICAL

[1] All studies had at least some methodological problems.

Multi-component exercise training

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-component	Control	Relative (95%CI)	Absolute		
Anxiety												
11	RCT	Serious[1]	No serious inconsistency[2]	No serious indirectness	Serious[3]	None	?	?	SMD = -0.45 (-0.71 to -0.18)	-	LOW	CRITICAL

[1] All studies had at least some methodological problems.

[2] I^2 = 63.3% due to one study.

[3] CI includes -0.5.

Relaxation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relaxation	Control	Relative (95%CI)	Absolute		
Anxiety												
3	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	?	?	SMD = -0.22 (-0.65 to 0.21)	-	LOW	CRITICAL

[1] All studies had at least some methodological problems.

[2] CI includes -0.5.

Cognitive behavioral treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT	Control	Relative (95%CI)	Absolute		
Anxiety												
7	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	?	?	SMD = -0.12 (-0.34 to 0.11)	-	MODERATE	CRITICAL
12	RCT	Serious[1]	Serious[2]	No serious indirectness	No serious imprecision	None	648	672	SMD = -0.23 (-0.42 to -0.04)	-	LOW	CRITICAL

[1] All studies had at least some methodological problems.

[2] I^2 62%, non-overlapping CI, and divergent results.

Mindfulness

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mindfulness**	**Wait list**	**Relative (95%CI)**	**Absolute**		
Anxiety												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	19	22	-	No significant difference	VERY LOW	CRITICAL

[1] Unclear risk of bias: unclear blinding, allocation concealment and ITT analysis (for this outcome).

[2] No data reported.

Pulmonary rehabilitation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pulmonary rehabilitation**	**Control**	**Relative (95%CI)**	**Absolute**		
Anxiety												
10	RCT	Serious[1]	No serious inconsistency[2]	No serious indirectness	Serious[3]	None	289	293	SMD = -0.53 (-0.82 to -0.23)	-	LOW	CRITICAL

[1] High risk of bias: most studies had inadequate blinding, allocation concealment and/or ITT analysis.

[2] I^2 = 63% due to one study.

[3] CI includes -0.5.

Distractive auditory stimuli

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DAS**	**Control**	**Relative (95%CI)**	**Absolute**		
Anxiety (STAI)												

1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	12	12	-	8w: 28.0 (SD 9.1) vs. 34.6 (9.1)	LOW	CRITICAL
Anxiety (SSAI)												
1	RCT	Serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	32	32	-	2nd session: DAS pre 32.41, post 24.00; relaxation pre 28.66, post 24.00; p=0.003	LOW	CRITICAL

[1] High risk of bias: no blinding, unclear randomization and allocation concealment; unclear ITT analysis.

[2] Small sample size; no information on change from baseline.

[3] High risk of bias: no blinding, unclear randomization and allocation concealment.

[4] Small sample size; no information on change from baseline.

Self-management

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Self-management**	**Usual care**	**Relative (95%CI)**	**Absolute**		
Anxiety (HADS)												
4	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	?	?	MD = -0.35 (-0.91 to 0.21)	-	MODERATE	CRITICAL

[1] All studies had at least some methodological issues.

Visual imagery technique

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**VIT**	**PMR**	**Relative (95%CI)**	**Absolute**		
Anxiety (HADS)												

1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	28	28	-	3.09 vs. 5.08 p<0.0001	LOW	CRITICAL

[1] High risk of bias: unclear blinding, unclear randomization and allocation concealment; unclear ITT analysis.

[2] Small sample size; no information on change from baseline.

Diazepam vs. promethazine vs. placebo

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Diazepam**	**Promethazine**	**Relative (95%CI)**	**Absolute**		
Anxiety: Morbid Anxiety Inventory												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	15	15	-	13.7 vs. 12.6 (vs. 11.5 placebo)	LOW	CRITICAL

[1] High risk of bias: unclear randomization and allocation concealment; no ITT analysis (3/18 drop-outs).

[2] No relative effect reported, no information on 95%CI.

SSRIs

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SSRI**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Anxiety												
3	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	21	22	-	See evidence tables	LOW	CRITICAL

[1] High risk of bias: three trials with methodological issues.

[2] Very small sample sizes. Estimation of SMD by updating the meta-analysis of Usmani 2011 with the data from Usmani 2018, using the Generic Inverse Variance method (and by inputting 0.00001 as SD for the control arm of Subbe 2014): SMD = -0.76 (95%CI -1.42 to -0.10, which includes -0.50).

TCA

Quality assessment	**No of patients**	**Effect**	**Quality**	**Importance**

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxepine	Placebo	Relative (95%CI)	Absolute		
Anxiety												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	9	9	SMD = -0.05 (-0.98 to 0.87)	-	VERY LOW	CRITICAL

[1] High risk of bias: unclear randomization, allocation concealment and blinding; no ITT analysis.

[2] SMD includes 0.5 and -0.5.

Azapirones

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Buspirone	Placebo	Relative (95%CI)	Absolute		
Anxiety												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	10	10	SMD = 0.17 (-0.71 to 1.05)	-	VERY LOW	CRITICAL

[1] High risk of bias: unclear randomization, allocation concealment and blinding; unclear ITT analysis.

[2] SMD includes 0.5 and -0.5.

Referenties

1. Baraniak A, Sheffield D. The efficacy of psychologically based interventions to improve anxiety, depression and quality of life in COPD: a systematic review and meta-analysis. Patient Educ Couns. 2011;83(1):29-36.
2. Coventry PA, Bower P, Keyworth C, Kenning C, Knopp J, Garrett C, et al. The effect of complex interventions on depression and anxiety in chronic obstructive pulmonary disease: systematic review and meta-analysis. PLoS ONE. 2013;8(4):e60532.
3. Gordon CS, Waller JW, Cook RM, Cavalera SL, Lim WT, Osadnik CR. Effect of Pulmonary Rehabilitation on Symptoms of Anxiety and Depression in COPD: A Systematic Review and Meta-Analysis. Chest. 2019;156(1):80-91.
4. Harrison SL, Lee A, Janaudis-Ferreira T, Goldstein RS, Brooks D. Mindfulness in people with a respiratory diagnosis: A systematic review. Patient Educ Couns. 2016;99(3):348-55.
5. Jolly K, Sidhu MS, Bates E, Majothi S, Sitch A, Bayliss S, et al. Systematic review of the effectiveness of community-based self-management interventions among primary care COPD patients. NPJ Prim Care Respir Med. 2018;28(1):44.
6. Lee AL, Desveaux L, Goldstein RS, Brooks D. Distractive auditory stimuli in the form of music in individuals with COPD: A systematic review. Chest. 2015;148(2):417-29.
7. Ma RC, Yin YY, Wang YQ, Liu X, Xie J. Effectiveness of cognitive behavioural therapy for chronic obstructive pulmonary disease patients: A systematic review and meta-analysis. Complement Ther Clin Pract. 2019;38:101071.

8. Mhaske M, Poovishnu DT, Jagtap V. Comparison of the effectiveness of visual imagery technique and progressive relaxation technique on anxiety and depression in subjects with moderate chronic obstructive pulmonary disease. Asian journal of pharmaceutical and clinical research [Internet]. 2018; 11(6):[318-23 pp.].
9. Simon S, Higginson I, Booth S, Harding R, Weingärtner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database Syst Rev [Internet]. 2016; (10).
10. Usmani Z, Carson-Chahhoud K, Esterman A, Smith B. A randomized placebo-controlled trial of paroxetine for the management of anxiety in chronic obstructive pulmonary disease (PAC study). Journal of multidisciplinary healthcare [Internet]. 2018; 11:[287-93 pp.].
11. Usmani ZA, Carson KV, Cheng JN, Esterman AJ, Smith BJ. Pharmacological interventions for the treatment of anxiety disorders in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2011(11):CD008483.
12. Usmani ZA, Carson KV, Heslop K, Esterman AJ, De Soyza A, Smith BJ. Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;2017(3).

Onderzoekvraag 4: Psychosociale zorg
Wat is het effect van (niet-)medicamenteuze behandeling op depressie bij mensen met COPD?

Patiënten Patiënten met COPD
Interventie Medicamenteuze en niet-medicamenteuze behandeling van depressieve symptomen of depressie
Comparator Andere interventie, placebo, geen behandeling
Outcome Kritisch: depressie

Evidence tabellen
Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Baraniak 2011	• Design: systematic review • Funding: not reported; CoI: not reported • Search date: Sep 2009 • Databases: Cochrane Library and MEDLINE, PsycARTICLES, PsycINFO, Web of Science • Study designs: comparative studies • N included studies: N=9, of which 6 RCTs	• Eligibility criteria: patients with a confirmed diagnosis of COPD without co-morbidities of asthma or other significant health problems impacting psychological intervention • Four studies included patients with moderate to severe COPD and one study included patients with mild to severe COPD; the remaining four studies confirmed diagnosis with spirometry, but did not report disease severity • Mean age: from 66-71 years	Psychologically based interventions	CRITICAL OUTCOMES • Depression: ○ Statistically significant improvement of post- vs. pre-intervention depression scores reported in 3 RCTs (Kunik 2001, Kunik 2007, de Godoy 2005) without significant differences between intervention groups ○ One RCT (Kunik 2001) found within group changes maintained at 44 weeks ○ Two studies (of which one RCT: Emery 1998) did not find within group differences nor pre-/ post-differences ○ Depression scores seemed to increase from baseline to post-intervention in one study (Rosser 1983), the greatest increase seen in the analytic psychotherapy group	Level of evidence: high risk of bias • Review process partially in duplicate (only data extraction 50%) • Limited to English studies • Combination of different study designs in meta-analysis
Beltman 2010	• Design: systematic review • Funding: not reported; CoI: none • Search date: Oct 2008	• Eligibility criteria: patients with somatic disease and depression or depressive symptoms, 18 years or older, without dementia or severe cognitive impairment	Cognitive–behavioural therapy	CRITICAL OUTCOMES • Depression: ○ Kunik 2008: SMD -0.03; 95%CI -0.28 to 0.23	Level of evidence: high risk of bias • Review process in duplicate • No language restriction

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Databases: Cochrane Central Register of Controlled Trials, PubMed and PsycINFO • Study designs: RCTs • N included studies: N=29 (1 with COPD patients)				
Coventry 2013	• Design: systematic review • Funding: funded by NIHR; CoI: authors declare not having CoI • Search date: Apr 2012 • Databases: CENTRAL, Medline, Embase, PsychINFO, CINAHL, ISI Web of Science, Scopus • Study designs: RCTs • N included studies: N=32	• Eligibility criteria: Individuals with confirmed COPD • Median age of 66.3 years; • Most patients had moderate or severe COPD; only one study with mild to moderate COPD patients	Single or multiple component interventions that include psychological and/or lifestyle components	CRITICAL OUTCOMES • Depression: ○ Overall SMD: -0.28 (95%CI -0.41 to -0.14) ○ Multi-component exercise training: SMD -0.47 (95%CI -0.66 to -0.28) ○ CBT: SMD -0.17 (95%CI -0.35 to 0.01) ○ Self-management education: SMD -0.00 (95%CI -0.17 to 0.16) ○ Relaxation: SMD -0.18 (95%CI -0.67 to 0.30) ○ Subgroup of samples with depression: SMD -0.29 (95%CI -0.49 to -0.10)	Level of evidence: high risk of bias • Only 5 studies with known depression at baseline (Bucknall 2012, de Godoy 2003, Hynninen 2010, Kunik 2008, Lamers 2010), depression scores were reported in 29 studies • Review process in duplicate • No language restriction
Ma 2019	• Design: systematic review • Funding: no funding received; CoI: reported as 'none' • Search date: July 2019 • Databases: PubMed, Cochrane library, EMBASE, Web of Science and China National Knowledge Infrastructure databases • Study designs: RCT • N included studies: N=16	• Eligibility criteria: individuals with an objective diagnosis of COPD according to pulmonary function or the GOLD criteria ○ Male: 63% ○ Age >=40 years • Duration/follow-up: 3 weeks – 1 year	Cognitive behavioural therapy (CBT)	CRITICAL OUTCOMES • Depression: ○ SMD = -0.29 (95%CI -0.40 to -0.19; p<0.001; I^2 46%) (14 studies)	Level of evidence: high risk of bias • Review process in duplicate • Limited to English and Chinese language

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Pollok 2018	• Design: systematic review • Funding: NIHR; CoI: declared none • Search date: Nov 2018 • Databases: MEDLINE, Embase, PsycINFO, CINAHL, AMED, and the Cochrane Library trials register (CENTRAL), ClinicalTrials.gov, the ISRCTN registry, and the World Health Organization International Clinical Trials Registry Platform • Study designs: published and unpublished RCTs • N included studies: N=4	• Eligibility criteria: patients with COPD, of age 40 years or older ○ Mean age: 58.7-71.2 years ○ Male: 55%	Pharmacological interventions	CRITICAL OUTCOMES • Depression: ○ TCA: MD -10.20, 95%CI -16.75 to -3.65; p=0.007 ○ SSRI: SMD 0.75, 95%CI -1.14 to 2.64; p=0.44	Level of evidence: high risk of bias • Review process in duplicate • No language restriction
Pollok 2019	• Design: systematic review • Funding: funded by NIHR; CoI: none • Search date: Nov 2018 • Databases: Cochrane Central Register of Controlled Trials, Ovid MEDLINE, Embase, PsycINFO, ClinicalTrials.gov, ISRCTN registry, World Health, Organization International Clinical Trials Registry Platform, grey literature databases • Study designs: RCTs • N included studies: N=13	• Eligibility criteria: patients diagnosed with COPD and depression or depressive symptoms, aged 40 years or older	Psychological therapies (PT)	CRITICAL OUTCOMES • Depression: change in depressive symptoms ○ PT vs. no intervention: ▪ all studies: SMD 0.19, 95%CI 0.05 to 0.33; p=0.009; 6 studies, N=764 ▪ clinically depressed only: SMD 0.20, 95%CI 0.02 to 0.37, p=0.03; 4 studies, N=499 ○ PT vs. education: SMD 0.23, 95%CI 0.06 to 0.41; p=0.010; 3 studies, N=507 ○ PT + PR vs. PR alone: SMD 0.37, 95%CI -0.00 to 0.74; p=0.05; 2 studies, N=112	Level of evidence: high risk of bias • Review process in duplicate • No language restriction

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Gordon 2019	• Design: systematic review • Funding: one author received Lung Foundation Australia/Boehringer-Ingelheim COPD Research Fellowship; CoI: authors declared no financial/ nonfinancial disclosures • Search date: February 2018 • Databases: MEDLINE (Ovid), CINAHL, PEDro, the Cochrane Library • Study designs: RCTs • N included studies: N=11	• Eligibility criteria: patients with COPD	Pulmonary rehabilitation	CRITICAL OUTCOMES • Depression: pooled SMD = -0.70 (95%CI -0.87 to -0.53); I^2 0% ○ program duration (< 8 vs. > 8 weeks) showed no significant difference (p=0.63)	Level of evidence: high risk of bias • 11 studies included, of which 10 were pooled in a meta-analysis • Review process in duplicate • Limited to English studies

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Alexopoulos 2013 & 2014	• Design: RCT • Funding: NIMH R01 HLB071992, P30 MH068638, P30 MH085943 and the Sanchez Foundation. R.S.N. partially supported by a grant from the Will Rogers Institute; CoI: One author received grant support from Forest Pharmaceuticals; has consulted to Hoffman-	• Eligibility criteria: Patients with severe COPD, meeting unipolar major depression criteria, Hamilton Rating Scale for depression score of 14 or more without other psychiatric diagnosis or sever cognitive impairment • *A priori* patient characteristics: ○ Mean age: 71.0 vs. 70.9 years ○ Depression (HRSD), mean score: 19.1 vs. 19.0 ○ FEV_1: 37.8 vs. 35.2%	Personalized intervention, 9 sessions (PID-C, N=67): The first session (30 minutes) with patients occurred prior to discharge. The remaining sessions (30 minutes) were conducted in the patients' homes at weeks 3, 4, 8, 12, 16, 20, 24, and 26. The first session focused on alliance and evaluation of risks to treatment engagement in individual patients. Subsequent sessions	CRITICAL OUTCOMES • Depression: ○ Remission of depression (HRSD ≤7): participants in the PID-C group had a significantly higher remission rate than the control group (p=0.016); HR 2.18 ○ PID-C had a significantly greater decline in HRSD between discharge and 28 weeks (effect size at 28 weeks 0.53; 95%CI 0.09-0.97; p=0.021) and a greater decline during follow-up (p=0.018) than the control group	Level of evidence: high risk of bias • Unclear randomisation and allocation concealment • No blinding of patients and clinicians; blinding of outcome assessors • No ITT analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	LaRoche, Lilly, Pfizer and Otsuka; and has served on speakers bureaus of Astra Zeneca, Avenir, Forest, Merck, Novartis and Sunovion • Setting: Weill-Cornell Institute, NY; acute in-patient rehabilitation unit and patients's home/ Community • Sample size: N=138 • Duration: 28 weeks		consisted of clinical state review and reinforcement of plans to address treatment engagement. The care managers telephoned the patients' physicians and informed them of the patients' status and adherence to treatment and rehabilitation. Physicians' recommendations for depression and COPD were given according to clinical indication and not influenced by PID-C managers vs. Treatment as usual (N=71)		
Alexopoulos 2016 & 2018	• Design: RCT • Funding: NIMH grants R01 MH076829 and P30 MH085943, and by the Sanchez Foundation; Dr. Novitch is partially supported by a grant from the Will Rogers Institute; CoI: one author serves at the speakers' bureaus of Takeda, Lundbeck, Otsuka, and Sunovion • Setting: Weill Cornell Medicine Institute, NY; acute inpatient rehabilitation and community	• Eligibility criteria: Patients with diagnosis of COPD who meet DSM-IV criteria for unipolar major depression, Hamilton Depression Rating Scale of 20 or greater • Exclusion: Patients having a DSM-IV other than unipolar major depression, significant cognitive impairment	Personalized intervention, 14 sessions over 26w (PID-C, N=50): - In-person approximately 45 min in-person sessions with patients and interaction with their physicians by telephone when needed - A manual guided care managers in evaluating barriers to adherence to physicians' recommendations in individual patients and plans to address them - The care managers remained in telephone contact with the patients' physicians and	CRITICAL OUTCOMES • Depression: ○ Both groups had similar course of depressive symptoms (treatment x time: p=0.4015) ○ Post-hoc one-sided hypothesis test indicated that PID-C was as good as PSA within 2.1 points based on HDRS difference between the two groups both at week 14 (0.129, 95% one sided CI:−∞, 1.87) and at week 26 (0.4752, 95% one sided CI:−∞, 2.06)	Level of evidence: high risk of bias • Unclear randomisation and allocation concealment • No blinding of patients and clinicians • ITT analysis done

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Sample size: N=101 • Duration: 26 weeks		informed them of any changes in the patients' status and any problems with adherence vs. Problem Solving-Adherence, 14 sessions over 26 weeks (PSA, N=51): - PSA integrates the personalized approach to adherence barriers of PID-C with development of problem solving skills. As in PID-C, the first targeted problems were related to adherence to treatment recommendations. Some adherence problems (e.g. misunderstanding, limited information) were addressed with education and direct instruction. However, hopelessness, helplessness and fatigue interfering with exercise and activities, social isolation and neglect of important relationships were addressed with problem solving skill development		
Mhaske 2018	• Design: RCT • Funding: not reported; CoI: declared having no CoI	• Eligibility criteria: Patients with moderate COPD, FEV/forced vital capacity <70% and FEV_1<80%, HADS-score 8-12,	Visual imagery technique (VIT; N=28) vs.	CRITICAL OUTCOMES • Depression: ○ DASS21 post-treatment: 6.27 vs. 8.69, t=3.504, p=0.0011	Level of evidence: high risk of bias • Unclear randomization and allocation method

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Setting: Krishna Hospital, Karad, India • Sample size: N=56 • Duration: not reported	being able to communicate and listen • Exclusion: receiving tricyclic antidepressants or other antipsychotic, having cardiovascular disease, uncontrolled hypertension, or evidence of evidence of neurological or musculoskeletal condition • *A priori* patient characteristics: ○ Mean age: 45 years ○ Men: 69%	Progressive relaxation technique (PRT; N=28)	○ HADS post-treatment: 3.45 vs. 5.30, t=5.519, p<0.0001	• Unclear blinding (but unlikely) • Higher DASS21-scores pre-treatment in VIT-group • 11 lost-to-follow-up, excluded from analysis

Abbreviations: 95%CI: 95% confidence interval; BMI: body mass index; CBT: cognitive behavioral treatment; CoI: conflicts of interest; COPD: chronic obstructive pulmonary disease; CRQ-M: chronic respiratory questionnaire – mastery; DAS: distractive auditory stimulus; DASS21: Depression Anxiety Stress Scale; FEV_1: forced expiratory volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HADS: Hospital Anxiety and Depression Scale; ICU: intensive care unit; IRR: incidence rate ratio; MD: mean difference; MRC: Medical Research Council; QOC: quality of communication; QOL: quality of life; RCT: randomized controlled trial; SD: standard deviation; SF-36: short form 36; SMD: standardized mean difference; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressants.

GRADE profielen

Psychological therapies

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Psychological therapy**	**Control**	**Relative (95%CI)**	**Absolute**		
Depression												
14	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	?	?	SMD = -0.29 (-0.49 to -0.10)	-	MODERATE	CRITICAL
6	RCT	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	381	383	SMD = 0.19 (0.05 to 0.33)	-	MODERATE	CRITICAL
3	RCT	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	None	250	257	SMD = 0.23 (0.06 to 0.41)	-	MODERATE	CRITICAL

[1] All studies had at least some methodological problems.
[2] Lack of blinding of participants and/or personnel. Also, blinding of outcome assessment was not reported in most of the studies, or the primary outcome was self-rated by participants who were not blinded to treatment allocation. Allocation concealment and selective reporting were assessed at unclear risk of bias in most of the studies.
[3] Lack of blinding of participants and/or personnel. Also, blinding of outcome assessment was reported in only one study or the primary outcome was self-rated by participants who were not blinded to treatment allocation. Allocation concealment was was an issue. Selective reporting was assessed at unclear risk of bias in all studies.

Psychological therapies + pulmonary rehabilitation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychological therapy + PR	Control	Relative (95%CI)	Absolute		
Depression												
2	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	53	61	SMD = 0.37 (-0.00 to 0.74)	-	LOW	CRITICAL

[1] Owing to the nature of the intervention, blinding of participants and research personnel, as well as blinding of outcome assessors was not feasible. The smaller study did not provide details describing methods of randomisation, allocation concealment.
[2] CI includes 0.5.

Multi-component exercise training

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-component	Control	Relative (95%CI)	Absolute		
Depression												
14	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	?	?	SMD = -0.47 (-0.66 to -0.28)	-	LOW	CRITICAL

[1] All studies had at least some methodological problems.
[2] CI includes -0.5.

Relaxation

Quality assessment							No of patients		Effect		Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relaxation	Control	Relative (95%CI)	Absolute		
Depression												
3	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	?	?	SMD = -0.18 (-0.67 to 0.30)	-	LOW	CRITICAL

[1] All studies had at least some methodological problems.

[2] CI includes -0.5.

Cognitive behavioral treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT	Control	Relative (95%CI)	Absolute		
Depression												
7	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	?	?	SMD = -0.17 (-0.35 to 0.01)	-	MODERATE	CRITICAL
14	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	707	718	SMD = -0.29 (-0.40 to -0.19)	-	MODERATE	CRITICAL

[1] All studies had at least some methodological problems.

Self-management training

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management	Usual care	Relative (95%CI)	Absolute		
Depression												
5	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	?	?	SMD = -0.00 (-0.17 to 0.16)	-	MODERATE	CRITICAL

[1] All studies had at least some methodological issues.

Personalized intervention vs. usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Personalized intervention**	**Usual care**	**Relative (95%CI)**	**Absolute**		
Remission of depression												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	67	71	-	HR 2.18 p=0.016	VERY LOW	CRITICAL

[1] Unclear risk of bias: unclear randomization and allocation concealment; no blinding and ITT analysis.

[2] No information to evaluate precision.

Personalized intervention vs. PSA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Personalized intervention**	**PSA**	**Relative (95%CI)**	**Absolute**		
Depression												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	50	51	-	F = 0.71 p=0.4015	VERY LOW	CRITICAL

[1] Unclear risk of bias: unclear randomization and allocation concealment; no blinding.

[2] No information to evaluate precision.

Pulmonary rehabilitation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pulmonary rehabilitation**	**Usual care**	**Relative (95%CI)**	**Absolute**		
Depression												
10	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	289	293	SMD = -0.70 (-0.87 to -0.53)	-	MODERATE	CRITICAL

[1] High risk of bias: most studies had inadequate blinding, allocation concealment and/or ITT analysis.

Visual imagery technique

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VIT	PMR	Relative (95%CI)	Absolute		
Depression (HADS)												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	28	28	-	3.45 vs. 5.30 p<0.0001	LOW	CRITICAL

[1] High risk of bias: unclear blinding, unclear randomization and allocation concealment; unclear ITT analysis.

[2] Small sample size; no information on change from baseline.

SSRIs

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRI	Placebo	Relative (95%CI)	Absolute		
Change in depressive symptoms												
2	RCT	Serious[1]	Very serious[2]	No serious indirectness	Very serious[3]	None	74	74	SMD 0.75 (-1.14 to 2.64)	-	VERY LOW	CRITICAL

[1] High risk of bias: unclear randomization (1 study) and allocation concealment (2 studies).

[2] I^2 95%, conflicting results and non-overlapping CI.

[3] CI includes 0.5 at both sides.

TCA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCA	Placebo	Relative (95%CI)	Absolute		
Change in depressive symptoms												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	13	17	MD -10.2 (-16.75 to -3.65)	-	LOW	CRITICAL

[1] High risk of bias: no information provided on allocation concealment and imbalanced dropout.

[2] Small sample size. Estimation of SMD: -1.03, 95%CI -1.80 to -0.25, which includes -0.5.

Referenties

1. Alexopoulos GS, Kiosses DN, Sirey JA, Kanellopoulos D, Novitch RS, Ghosh S, et al. Personalised intervention for people with depression and severe COPD. Br J Psychiatry. 2013;202(3):235-6.
2. Alexopoulos GS, Kiosses DN, Sirey JA, Kanellopoulos D, Seirup JK, Novitch RS, et al. Untangling therapeutic ingredients of a personalized intervention for patients with depression and severe COPD. Am J Geriatr Psychiatry. 2014;22(11):1316-24.
3. Alexopoulos GS, Sirey JA, Banerjee S, Jackson DS, Kiosses DN, Pollari C, et al. Two Interventions for Patients with Major Depression and Severe Chronic Obstructive Pulmonary Disease: Impact on Dyspnea-Related Disability. Am J Geriatr Psychiatry. 2018;26(2):162-71.
4. Alexopoulos GS, Sirey JA, Banerjee S, Kiosses DN, Pollari C, Novitch RS, et al. Two Behavioral Interventions for Patients with Major Depression and Severe COPD. Am J Geriatr Psychiatry. 2016;24(11):964-74.
5. Baraniak A, Sheffield D. The efficacy of psychologically based interventions to improve anxiety, depression and quality of life in COPD: a systematic review and meta-analysis. Patient Educ Couns. 2011;83(1):29-36.
6. Beltman MW, Oude Voshaar RC, Speckens AE. Cognitive-behavioural therapy for depression in people with a somatic disease: Meta-analysis of randomised controlled trials. Br J Psychiatry. 2010;197(1):11-9.
7. Coventry PA, Bower P, Keyworth C, Kenning C, Knopp J, Garrett C, et al. The effect of complex interventions on depression and anxiety in chronic obstructive pulmonary disease: systematic review and meta-analysis. PLoS ONE. 2013;8(4):e60532.
8. de Godoy DV, de Godoy RF. A randomized controlled trial of the effect of psychotherapy on anxiety and depression in chronic obstructive pulmonary disease. Arch Phys Med Rehabil. 2003;84(8):1154-7.
9. Emery CF, Schein RL, Hauck ER, MacIntyre NR. Psychological and cognitive outcomes of a randomized trial of exercise among patients with chronic obstructive pulmonary disease. Health Psychol. 1998;17(3):232-40.
10. Gordon CS, Waller JW, Cook RM, Cavalera SL, Lim WT, Osadnik CR. Effect of Pulmonary Rehabilitation on Symptoms of Anxiety and Depression in COPD: A Systematic Review and Meta-Analysis. Chest. 2019;156(1):80-91.
11. Kunik ME, Azzam PN, Souchek J, Cully JA, Wray NP, Krishnan LL, et al. A practical screening tool for anxiety and depression in patients with chronic breathing disorders. Psychosomatics. 2007;48(1):16-21.
12. Kunik ME, Braun U, Stanley MA, Wristers K, Molinari V, Stoebner D, et al. One session cognitive behavioural therapy for elderly patients with chronic obstructive pulmonary disease. Psychol Med. 2001;31(4):717-23.
13. Ma RC, Yin YY, Wang YQ, Liu X, Xie J. Effectiveness of cognitive behavioural therapy for chronic obstructive pulmonary disease patients: A systematic review and meta-analysis. Complement Ther Clin Pract. 2019;38:101071.
14. Mhaske M, Poovishnu DT, Jagtap V. Comparison of the effectiveness of visual imagery technique and progressive relaxation technique on anxiety and depression in subjects with moderate chronic obstructive pulmonary disease. Asian journal of pharmaceutical and clinical research [Internet]. 2018; 11(6):[318-23 pp.].
15. Pollok J, van Agteren JE, Carson-Chahhoud KV. Pharmacological interventions for the treatment of depression in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2018;12:CD012346.
16. Pollok J, van Agteren JE, Esterman AJ, Carson-Chahhoud KV. Psychological therapies for the treatment of depression in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2019;3:CD012347.
17. Rosser R, Denford J, Heslop A, Kinston W, Macklin D, Minty K, et al. Breathlessness and psychiatric morbidity in chronic bronchitis and emphysema: a study of psychotherapeutic management. Psychol Med. 1983;13(1):93-110.

Onderzoeksvraag 5: Symptomen
Wat is het effect van niet-medicamenteuze behandeling op dyspneu bij mensen met COPD?

Patiënten	Patiënten met gevorderde COPD
Interventie	Niet-medicamenteuze behandeling: a. ademhalingsoefeningen, b. mind-body interventies en ontspanningsoefeningen, c. hulpmiddelen bij het lopen, d. ventilator, e. breathlessness support services, f. zuurstof
Comparator	Andere interventie, geen interventie
Outcome	Kritisch: dyspneu, kwaliteit van leven Belangrijk: fysiek functioneren, inspanningstolerantie

a. Ademhalingsoefeningen

Evidence tabellen
Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Beaumont 2018	• Design: systematic review (CRD42015017638) • Funding: not reported; CoI: authors declared having no CoI • Search date: Dec 2017 • Databases: PubMed, Science direct, Cochrane library, Web of science, Pascal • Study designs: RCTs, CCTs, cohort studies • N included studies: N=43 (38 RCTs)	• Eligibility criteria: patients with stable COPD or with acute COPD exacerbations	Inspiratory muscle training (IMT) using threshold devices	CRITICAL OUTCOMES • Dyspnoea: ○ No significant difference of IMT vs control on Borg-scale: MD -0.52 (11 studies; 95%CI -1.09 to 0.05; p=0.07; I^2 94%) ○ Significant effect on Baseline-Transition Dyspnea Index: MD 2.30 (5 studies; 95%CI 1.67 to 2.93; p<0.00001; I^2 38%) ○ CRQ – dyspnoea: clinically relevant decrease of dyspnoea (not reported) • Quality of life: ○ SGRQ: MD -2.40 (6 studies; 95%CI -4.89 to 0.09, p=0.06; I^2 0%) ○ CRQ: MD 2.7 (4 studies; 95%CI -0.24 to 5.64, p=0.07; I^2 62%) IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance:	Level of evidence: high risk of bias • Review process in duplicate • Unclear language restrictions • Quality assessment with Pedro-scale, only numerical result reported • Mixed RCTs and CCTs in their meta-analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				○ 6MWD: MD 42.68 (16 studies; 95%CI 16.9 to 68.47, p=0.001; I² 92%) ○ 12MWD: MD 114.55 (95%CI -89.54 to 318.63, p=0.27) ○ ISWT: MD 53.96 (95%CI -32.19 to 140.11, p=0.22) ○ CPET: 4 studies showed improvement, 1 study showed a decrease in workload	
Borge 2014	• Design: systematic review • Funding: not reported; CoI: authors declared not having CoI • Search date: Dec 2013 • Databases: PubMed, Ovid, CINAHL, PsycINFO, AMED, Cochrane and PEDro • Study designs: systematic reviews • N included studies: N=7	• Eligibility criteria: patients over 18 years with COPD	Controlled breathing exercises and respiratory muscle training	CRITICAL OUTCOMES • Dyspnoea: ○ Gosselink 2011 ▪ 14 RCTs comparing inspiratory muscle training with a control: significant effect (p<0.001) in favour of inspiratory muscle training on dyspnoea, summary effect size of -0.45 (95%CI -0.66 to -0.24), corresponding to -0.9 on the Borg-scale ▪ 4 RCTs using Transition Dyspnea Index: significant effect of inspiratory muscle training, summary effect size 1.58 (95%CI 0.86-2.3; p<0.001) ○ Thomas 2010 ▪ 3 RCTs that compared those who received respiratory muscle training (inspiratory muscle training and expiratory muscle training) at home with controls: MD 2.36 (95%CI 0.76-3.96) on the Baseline and Transition Dyspnea Indexes (BDI/TDI) score ○ Geddes 2008: ▪ Borg-scale; 4 studies, WMD -1.76 (95%CI -2.35 to -1.16) ○ O'Brien 2008: inspiratory muscle training versus exercise or a combination of exercises and inspiratory muscle training; unclear effect	Level of evidence: high risk of bias • Review of reviews • Review process partly in duplicate; however unclear exactly which phases were duplicated • Language restrictions unclear

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				○ Shoemaker 2009: inspiratory muscle training improved dyspnoea ○ Holland 2012: ▪ Pursed-lip breathing: 2 RCTs, MD -12.94 (95%CI -22.29 to -3.60) on Hiratsuka Scale ▪ 1 RCT showed an effect on shortness of breath in favour of pursed lip breathing ○ Roberts 2009: 40% of dyspnoea was relieved when pursed-lip breathing was used • Quality of life: ○ Gosselink 2011: CRQ, 9 studies, summary effect size 0.34 (95%CI 0.09 to 0.6) ○ Geddes 2008: CRQ total score; 2 studies, WMD 0.33 (95%CI 0.19-0.47) ○ O'Brien 2008: inspiratory muscle training versus exercise or a combination of exercises and inspiratory muscle training, unclear effect ○ Shoemaker 2009: inspiratory muscle training improved QOL ○ Holland 2012: ▪ 1 RCT showed an effect on shortness of QOL in favour of pursed lip breathing ▪ Two trials on diaphragmatic breathing and four on yoga breathing showed effects only in one study in each exercise on disease-related QOL IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: not reported	
Mayer 2018	• Design: systematic review (CRD42015025903) • Funding: not reported; CoI: none declared	• Eligibility criteria: patients with COPD; age over 40; no other pulmonary diseases, heart	Pursed lip breathing (PLB)	CRITICAL OUTCOMES • Dyspnoea: ○ Visual Analogue Scale: MD -0.11 (2 studies; 95%CI -1.05 to 0.83, p=0.81; I^2 0%)	Level of evidence: high risk of bias • Review process in duplicate

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Search date: May 2016 • Databases: PEDro, EMBASE, MEDLINE via OVID, and EBSCO • Study designs: RCTs, quasi-RCTs, cross-over design • N included studies: N=8	disease, or neuromuscular disease		○ Borg-scale: MD -0.15 (5 studies; 95%CI -0.45 to 0.15, p=0.34; I² 0%) • Quality of life: not reported IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: ○ 6MWD: MD 6.14 (2 studies; 95%CI -35.03 to 47.30, p=0.77; I² 33%) ○ Oxygen saturation end-exercise: MD 0.44 (6 studies; 95%CI -0.43 to 1.32, p=0.32; I² 0%)	• Language restriction: English, Spanish, Portuguese • Quality assessment with Pedro-scale, only numerical result reported
Neves 2014	• Design: systematic review • Funding: not reported; CoI: disclosed no CoI • Search date: Feb 2013 • Databases: MEDLINE, Embase, LILACS, PEDro, and Cochrane CENTRAL • Study designs: RCTs • N included studies: N=5 (111 patients)	• Eligibility criteria: patients with COPD	Expiratory muscle training (EMT) EMT plus IMT	CRITICAL OUTCOMES • Dyspnoea: ○ EMT vs. control: MD 0.15 (2 studies; 95%CI -0.77 to 1.08; I² 0%) • Quality of life: not reported IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: 6MWD ○ EMT vs control: MD 29.01 (3 studies; 95%CI -39.62 to 97.65; I² 0%)	Level of evidence: high risk of bias • Review process in duplicate • Unclear language restriction

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Borge 2015	• Design: RCT • Funding: Norwegian Extra Foundation for Health and Rehabilitation through EXTRA funds, the Norwegian Nurses'	• Eligibility criteria: patients with moderate to severe COPD, MRC dyspnoea scale >=1 and able to communicate in Norwegian • Exclusion criteria: change in medication last 4 weeks, diagnosed with cancer, attending	Guided deep breathing (N=51) vs. Music listening (N=50)	CRITICAL OUTCOMES • Dyspnoea: ○ GRC scale for breathlessness: ▪ After 4 weeks: 3.2 vs. 1.8 vs. 1.9; positive significant change vs. music (p=0.03)	Level of evidence: high risk of bias • Person who was not involved in the project was responsible for randomizing the participants

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Organisation (NNO); CoI: None declared • Setting: Lovisenberg Diaconal Hospital, Norway • Sample size: N=150 • Duration: 4 months, Jul 2011 - Sep 2013	a pulmonary rehabilitation course or a competing study, receiving pulmonary rehabilitation or abuse of drug or alcohol • *A priori* patient characteristics: ○ Mean age: 67y ○ Men: 50% ○ FEV_1 predicted: 58%	Vs. Still sitting (N=49)	▪ After 4 months: 2.8 vs. 1.5 vs. 2.4; significantly different from music (p=0.04), but not from still sitting • Quality of life: ○ SGRQ total score: no significant differences found after 4 weeks and 4 months: ▪ After 4 weeks: 48.5 vs. 46 vs. 38.3 ▪ After 4 months: 49.7 vs. 44.9 vs. 37.6 IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: not reported	• Blinding of patients and researchers, but no guarantee • No ITT analysis
Gu 2018	• Design: RCT • Funding: supported by National Key R&D Program of China (2017YFC1310601); National Natural Science Foundation of China and Canadian Institutes of Health Research (NSFC-CIHR) (81361128004); the Guangzhou Healthcare Collaborative Innovation Major Project (201604020012); Natural Science Foundation of Guangdong Province (2015A030310497);Postdoctoral Scientific Research Start-up Fund of Guangzhou (19800226); CoI: declared none	• Eligibility criteria: patients with stable, moderate or severe COPD symptoms confirmed by clinical presentation and spirometric testing, being 50 years or older, with post-bronchodilator FEV_1 <80% predicted and FEV_1/FVC ratio <70%; without acute exacerbation nor systemic use of glucocorticosteroids in the past 4 weeks • Exclusion criteria: history or diagnosis of bronchial asthma, being an ex-smoker, participation in previous PR programs, or disorders involving pleural cavity, thoracic wall, bone and joint or neurological or muscular system • *A priori* patient characteristics: ○ Mean age: 66 years ○ Men: 97%	Novel breathing training with rapid deep inspiration and prolonged expiration (N=22) vs. Diaphragmatic breathing training (N=23) vs. Control (N=20)	CRITICAL OUTCOMES • Dyspnoea: Change in mMRC from baseline to 8w ○ Group A: 0.86 +/- 0.71 (p<0.001 vs. group C) ○ Group B: 0.86 +/- 0.69 (p<0.001 vs. group C) ○ Group C: 0.00 +/- 0.32 • Quality of life: SGRQ, total score, change from baseline to 8w ○ Group A: 12.4 +/- 6.52 (p<0.001 vs. group C) ○ Group B: 12.52 +/- 9.89 (p<0.001 vs. group C) ○ Group C: 0.40 +/- 6.28 IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: 6MWD ○ Group A: 51.77 +/- 52.77 (p<0.001 vs. group C) ○ Group B: 49.04 +/- 63.11 (p<0.001 vs. group C) ○ Group C: 1.65 +/- 17.47	Level of evidence: high risk of bias • Unclear randomisation and allocation method • Unclear blinding (but unlikely for patients) • Drop-outs: 20%

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Setting: outpatient clinic, First Affiliated Hospital of Guangzhou Medical University, China • Sample size: N=65 • Duration: Apr to Dec 2013	○ FEV_1 (L):0.96 ○ FEV_1/FVC: 41.9% ○ 6MWD: 424 m ○ mMRC: 2.58			
Tan 2019	• Design: RCT • Funding: Research Acculturation Grant Scheme, Ministry of Education Malaysia; CoI: authors declared no CoI • Setting: University Malaya Medical Centre, Malaysia • Sample size: N=63 • Duration: Aug 2017 -Mar 2018	• Eligibility criteria: adult patients with moderate to severe dyspnea on Modified Borg Dyspnea Scale >= 3 due to lung cancer, COPD, and asthma • Exclusion: confusion based on Confusion Assessment Method, non-communicative or uninterested • *A priori* patient characteristics: ○ Mean age: 64 years ○ Men: 59% ○ COPD 25%, lung cancer 51%	20-minute mindful breathing with standard care (N=32) vs. Standard care alone (N=31)	CRITICAL OUTCOMES • Dyspnoea: ○ Differences in modified Borg Dyspnea Scale: ▪ T5-T0: median (IQR) 0 (1.5) vs. 0 (0), p=0.034 ▪ T20-T0: -1.0 (2.0) vs. 0 (1.0), p=0.076 • Quality of life: not reported IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: not reported	Level of evidence: high risk of bias • Computer-generated random numbers • Unclear allocation concealment • Not blinded • Only data for COPD reported here

GRADE profielen

Inspiratory muscle training (IMT)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IMT	Control	Relative (95%CI)	Absolute		
Dyspnoea: Borg-scale												
11	RCT	Very serious[1]	Very serious[2]	No serious indirectness	Serious[3]	None	159	153	MD -0.52 -1.09 to 0.05	-	VERY LOW	CRITICAL
14	RCT	?	?	?	?	?	?	?	Summary effect size -0.45 -0.66 to -0.24	-	?	CRITICAL

Dyspnoea: Baseline-Transition Dyspnea Index												
5	RCT	Very serious[4]	No serious inconsistency	No serious indirectness	No serious imprecision	None	75	71	MD 2.30 1.67 to 2.93	-	LOW	CRITICAL
4	RCT	?	?	?	?	?	?	?	Summary effect size 1.58 0.86 to 2.30	-	?	CRITICAL
Dyspnoea: Change in mMRC from baseline to 8w												
1	RCT	Serious[5]	No serious inconsistency	No serious indirectness	Serious[6]	None	22	20	-	0.86 vs. 0.00 p<0.001	LOW	CRITICAL
Quality of life: SGRQ												
6	RCT	Very serious[7]	No serious inconsistency	No serious indirectness	Serious[8]	None	83	78	MD -2.40 -4.89 to 0.09	-	VERY LOW	CRITICAL
1	RCT	Serious[5]	No serious inconsistency	No serious indirectness	Serious[9]	None	22	20	-	12.4 vs. 0.40 p<0.001	LOW	CRITICAL
Quality of life: CRQ												
4	RCT	Serious[10]	No serious inconsistency	No serious indirectness	Serious[11]	None	56	58	MD 2.7 -0.24 to 5.64	-	LOW	CRITICAL
9	RCT	?	?	?	?	?	?	?	Summary effect size 0.34 0.09 to 0.6	-	?	CRITICAL
Exercise tolerance: 6MWD												
16	RCT	Very serious[14]	Serious[13]	No serious indirectness	No serious imprecision	None	330	285	MD 42.68 16.9 to 68.47	-	VERY LOW	IMPORTANT
1	RCT	Serious[5]	No serious inconsistency	No serious indirectness	Serious[14]	None	22	20	-	51.77 vs. 1.65 p<0.001	LOW	IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: Pedro-score ranging from 3 to 8/10; 1 CCT included in meta-analysis (Tout 2013).

[2] I^2 94%, several non-overlapping CIs.

[3] Estimated SMD = -0.63 (95%CI -1.33 to 0.06); CI includes -0.5.

[4] High risk of bias: Pedro-score ranging from 4 to 6/10; 1 CCT included in meta-analysis (Garcia 2008).
[5] High risk of bias: unclear randomization, allocation concealment and blinding, 20% drop-outs.
[6] Estimated SMD = 0.32 (95%CI -0.29 to 0.93); CI includes 0.5.
[7] High risk of bias: Pedro-score ranging from 4 to 8/10; 2 CCTs included in meta-analysis (Garcia 2008, Tout 2013).
[8] Estimated SMD = -0.28 (95%CI -0.60 to 0.04); CI includes -0.5; optimal information size not reached.
[9] Estimated SMD = 0.40 (95%CI -0.21 to 1.01); CI includes 0.5.
[10] High risk of bias: Pedro-score ranging from 5 to 6/10.
[11] Estimated SMD = 0.55 (95%CI -0.08 to 1.18); CI includes 0.5.
[12] High risk of bias: Pedro-score ranging from 3 to 8/10; 1 CCT included in meta-analysis (Tout 2013).
[13] I^2 92%, most studies are in favour of IMT.
[14] Estimated SMD = 0.26 (95%CI -0.35 to 0.87); CI includes 0.5.

Expiratory muscle training (EMT)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EMT**	**Control**	**Relative (95%CI)**	**Absolute**		
Dyspnoea												
2	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	17	15	MD 0.15 -0.77 to 1.08	-	LOW	CRITICAL
Quality of life												
0	No evidence											CRITICAL
Exercise tolerance												
3	RCT	Serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	30	25	MD 29.01 -39.62 to 97.65	-	VERY LOW	IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: unclear allocation concealment (2 studies), no ITT analysis (2 studies).
[2] Estimated SMD = 0.27 (95%CI -0.46 to 0.99); CI includes 0.5.
[3] High risk of bias: unclear allocation concealment (3 studies), no ITT analysis (1 study).
[4] Estimated SMD = 0.19 (95%CI -0.34 to 0.73); CI includes 0.5.

EMT + IMT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EMT + IMT**	**Control**	**Relative (95%CI)**	**Absolute**		
Dyspnoea: Baseline-Transition Dyspnea Index												
3	RCT	?	?	?	?	?	?	?	MD 2.36 0.76 to 3.96	-	?	CRITICAL
Quality of life												
0	No evidence											CRITICAL
Exercise tolerance												
0	No evidence											IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

Pursed lips breathing

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PLB**	**Control**	**Relative (95%CI)**	**Absolute**		
Dyspnoea: VAS												
2	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	22	22	MD -0.11 -1.05 to 0.83	-	VERY LOW	CRITICAL
Dyspnoea: Borg-scale												
5	RCT	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious[4]	186	186	MD -0.15 -0.45 to 0.15	-	VERY LOW	CRITICAL
Dyspnoea: Hiratsuka Scale												
2	RCT	?	?	?	?	?	?	?	MD -12.94 -22.29 to -3.60	-	?	CRITICAL
Quality of life												
0	No evidence											CRITICAL

Exercise tolerance: 6MWD											
2	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[6]	None	39	39	MD 6.14 -35.03 to 47.30	-	LOW	IMPORTANT
Exercise tolerance: Oxygen saturation end-exercise											
6	RCT	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	182	182	MD 0.44 -0.43 to 1.32	-	MODERATE	IMPORTANT
Physical functioning											
0	No evidence											IMPORTANT

[1] High risk of bias: Pedro-score 5/10 for all studies.

[2] Estimated SMD = -0.03 (95%CI -0.63 to 0.56); CI includes -0.5 and 0.5.

[3] High risk of bias: range Pedro-score 4-5/10.

[4] Probably input error: same results (from study with most weight) twice counted in meta-analysis.

[5] High risk of bias: range Pedro-score 3-5/10.

[6] Estimated SMD = 0.08 (95%CI -0.45 to 0.61); CI includes 0.5.

Diaphragmatic breathing training

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DBT**	**Usual care**	**Relative (95%CI)**	**Absolute**		
Dyspnoea: change in mMRC from baseline to 8w												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	23	20	-	0.86 vs. 0.00 p<0.001	LOW	CRITICAL
Quality of life: SGRQ, total score, change from baseline to 8w												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	23	20	-	12.52 vs. 0.40 p<0.001	LOW	CRITICAL
Exercise tolerance: 6MWD												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	23	20	-	49.04 vs. 1.65 p<0.001	LOW	CRITICAL
Physical functioning												

0	No evidence	IMPORTANT

[1] High risk of bias: unclear randomization, allocation concealment and blinding, 20% drop-outs.

[2] Estimated SMD = 0.32 (95%CI -0.28 to 0.93); CI includes 0.5.

[3] Estimated SMD = 0.30 (95%CI -0.30 to 0.90); CI includes 0.5.

[4] Estimated SMD = 0.20 (95%CI -0.40 to 0.80); CI includes 0.5

Guided deep breathing

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GDB**	**Control**	**Relative (95%CI)**	**Absolute**		
Dyspnoea: GRC scale for breathlessness at 4 w												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	46	48/45	-	Positive significant change vs. music (p=0.03)	LOW	CRITICAL
Dyspnoea: GRC scale for breathlessness at 4 m												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	45	42/43	-	Significantly different from music (p=0.04), but not from still sitting	LOW	CRITICAL
Quality of life: SGRQ at 4 w												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	47	47/46	-	48.5 vs. 38.3	LOW	CRITICAL
Quality of life: SGRQ at 4 m												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[5]	None	46	43/41	-	49.7 vs. 37.6	LOW	CRITICAL
Exercise tolerance												
0	No evidence											IMPORTANT
Physical functioning												

0	No evidence	IMPORTANT

[1] High risk of bias: no ITT analysis.

[2] Vs. music: estimated SMD = 0.52 (95%CI 0.11 to 0.93); CI includes 0.5; vs. still sitting: estimated SMD = 0.44 (95%CI 0.03 to 0.86); CI includes 0.5.

[3] Vs. music: estimated SMD = 0.46 (95%CI 0.04 to 0.89); CI includes 0.5; vs. still sitting: estimated SMD = 0.13 (95%CI -0.29 to 0.54); CI includes 0.5.

[4] Vs. music: estimated SMD = 0.13 (95%CI -0.27 to 0.54); CI includes 0.5; vs. still sitting: estimated SMD = 0.51 (95%CI 0.09 to 0.92); CI includes 0.5.

[5] Vs. music: estimated SMD = 0.23 (95%CI -0.18 to 0.65); CI includes 0.5; vs. still sitting: estimated SMD = 0.59 (95%CI 0.16 to 1.02); CI includes 0.5.

Mindful breathing

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MB**	**Control**	**Relative (95%CI)**	**Absolute**		
Dyspnoea: modified Borg Dyspnea Scale												
1	RCT	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	32	31	-	T5-T0: median (IQR) 0 (1.5) vs. 0 (0), p=0.034 T20-T0: -1.0 (2.0) vs. 0 (1.0), p=0.076	VERY LOW	CRITICAL
Quality of life												
0	No evidence											CRITICAL
Exercise tolerance												
0	No evidence											IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: unclear allocation concealment, no blinding of patients and clinicians.

[2] 25% had COPD.

[3] Insufficient information to evaluate precision; rule of thumb > 400.

b. Mind-body interventies en ontspanningsoefeningen

Evidence tabllen

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Gendron 2018	• Design: systematic review • Funding: no funding received; CoI: one author received grants from different pharmaceutical companies • Search date: Jul 2017 • Databases: CENTRAL, MEDLINE, Embase, CINAHL, AMED, PsycINFO, China National Knowledge Infrastructure (CNKI), WANGFAN, VIP, and SinoMed (Chinese Biomedical Literature Database, Chinese Medical Science Literature Database, and Beijing Union Medical Doctor and Master Thesis Database), Indian Biomedical Journals Database (IndMED) • Study designs: RCTs • N included studies: N=10 (762 patients)	• Eligibility criteria: adult patients with clinical diagnosis of COPD • *A priori* patient characteristics: ○ Age: 55-88y ○ Male: 78%	Active mind body movement therapies +/- pulmonary rehabilitation vs. Pulmonary rehabilitation alone	CRITICAL OUTCOMES • Dyspnoea: ○ AMBMT vs. PR: ▪ mMRC: MD 0.00 (95%CI -0.37 to 0.37; 2 studies; N=127) ▪ Borg-scale: MD -0.44 (95%CI -0.88 to 0.00; 1 study; N=139) ▪ CRQ dyspnoea subscale: MD -0.21 (95%CI -2.81 to 2.38; 1 study; N=11) ○ AMBMT + PR vs. PR alone: ▪ CRQ dyspnoea subscale: MD 0.04 (95%CI -2.18 to 2.26; 1 study; N=80) • Quality of life: ○ AMBMT vs. PR: ▪ SGRQ total score: MD -5.83 (95%CI -8.75 to -2.92; 3 studies, N=249) ▪ CAT: MD 6.58 (95%CI -9.16 to - 4.00; 1 study; N=74) ○ AMBMT + PR vs. PR alone: ▪ SF-36 general health: MD 5.42 (95%CI 3.82 to 7.02; 1 study; N=80) ▪ SF-36 mental health: MD 3.29 (95%CI 1.45 to 4.95; 1 study; N=80) ▪ SGRQ total score: MD -2.57 (95%CI -7.76 to 2.62; 1 study; N=192) IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: ○ 6MWD:	Level of evidence: high risk of bias • Review process in duplicate • No language restriction • Most included studies (8/10) considered unstructured walking training as equal to pulmonary rehabilitation

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				▪ Tai chi: 3 studies, N=253; MD 19.22 (95%CI -1.86 to 40.30) ▪ Qigong: 3 studies, N=172; MD -0.16 (95%CI -10.11 to 9.80) ▪ Yoga: 1 study, N=11; MD -69.30 (95%CI -117.73 to -20.87) ▪ AMBMT + PR vs. PR alone: 2 studies, N=272; MD 14.09 (95%CI -3.68 to 31,86) ○ Incremental cycle ergometry: 1 study, N=36; MD 55 (95%CI -157.82 to 267.82)	
Ngai 2016	• Design: systematic review • Funding: no funding received; CoI: authors declared having no CoI • Search date: Sep 2015 • Databases: CENTRAL, MEDLINE, EMBASE, CINAHL, AMED, PsycINFO , Wanfang Data, Chinese Medical Current Contents (CMCC), Chinese Biomedical Database (CBM), China Journal Net (CJN) and China Medical Academic Conference (CMAC) • Study designs: RCTs • N included studies: N=12 (984 patients)	• Eligibility criteria: patients clinically diagnosed with COPD • *A priori* patient characteristics: ○ Mean age: 61 – 74 years	Tai Chi	CRITICAL OUTCOMES • Dyspnoea: ○ Tai Chi vs usual care: ▪ Borg-scale: MD -0.2 (1 study; N=137; 95%CI -0.67 to 0.27) ▪ UCSD SOB: MD 5 (1 study; N=10; 95%CI -11.62 to 21.62) ▪ mMRC: MD -0.15 (2 studies; N=96; 95%CI -0.56 to 0.26; I^2 61%) ▪ CRQ dyspnoea: MD 0.05 (2 studies; N=48; 95%CI -1.32 to 1.42; I^2 82%) ○ Tai Chi + breathing exercise vs breathing exercise: ▪ Borg-scale: MD -1.3 (1 study; N=80; 95%CI -2.02 to -0.58) • Quality of life: ○ Tai Chi vs usual care: ▪ SGRQ total score: MD -7.85 (3 studies; N=233; 95%CI -16.53 to 0.83; I^2 85%) ▪ CRQ total: MD 0.41 (2 studies; N=48; 95%CI -0.54 to 1.35; I^2 49%) ▪ CRQ mastery: MD 0.89 (2 studies; N=48; 95%CI 0.3 to 1.47; I^2 0%)	Level of evidence: high risk of bias • Review process in duplicate • No language restriction

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				○ Tai Chi + breathing exercise vs breathing exercise: ▪ SGRQ total: MD -1.32 (2 studies; N=120; 95%CI -5.92 to 3.28; I^2 0%) ○ Tai Chi + exercise vs exercise: ▪ SGRQ total: MD -3.76 (1 study; N=192; 95%CI -8.72 to 1.2) IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: ○ Tai Chi vs usual care: ▪ 6MWD: MD 29.64 (6 studies; N=318; 95%CI 10.52 to 48.77; I^2 59%) ▪ ISWT: MD 2 (1 study; N=38; 95%CI -95.26 to 99.26) ▪ ESWT: MD 373 (1 study; N=38; 95%CI 135.42 to 610.58) ▪ Exercise duration: MD 1 (1 study; N=10; 95%CI -1.1 to 3.1) ▪ Peak VO2: MD -2 (1 study; N=10; 95%CI -5.76 to 1.76) ○ Tai Chi + breathing exercise vs breathing exercise: 6MWD: MD 22 (1 study; N=60; 95%CI -6 to 50) ○ Tai Chi + exercise vs exercise: 6MWD: MD 1.5 (1 study; N=192; 95%CI -18.76 to 21.76)	
Wu 2018	• Design: systematic review • Funding: not reported; CoI: reported having no CoI • Search date: Aug 2017	• Eligibility criteria: Patients with COPD • *A priori* patient characteristics: ○ Mean age: 45 - 74.1y ○ FEV_1 predicted: 36.75 - 59.12%	Meditative movement	CRITICAL OUTCOMES • Dyspnoea: ○ Meditative movement vs non-exercise: ▪ CRQ dyspnoea score: 3 months MD 0.9 (2 studies; N=48; 95%CI 0.51 to 1.29, I^2 0%) ○ Meditative movement vs walking exercise:	Level of evidence: high risk of bias • Selection and quality appraisal by two reviewers; data extraction unclear • No language restrictions

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Databases: PubMed, Web of Science, EMBASE, CENTRAL • Study designs: RCTs • N included studies: N=16 (1176 patients)			▪ CRQ dyspnoea score: 6 months MD 0.46 (2 studies; N=206; 95%CI -0.28 to 1.20; I² 90%) • Quality of life: ○ Meditative movement vs non-exercise: ▪ CRQ total score: 3 months MD 1.92 (2 studies; N=48; 95%CI 0.54 to 3.31, I² 42) ▪ CRQ mastery: 3 months MD 1.57 (2 studies; N=48; 95%CI -0.49 to 3.62; I² 96%) ○ Meditative movement vs walking exercise: ▪ CRQ mastery: 6 months MD 0.00 (2 studies; N=206; 95%CI -0.32 to 0.33, I² 55%) IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: ○ 6MWD ▪ Meditative movement vs non-exercise: at 3 months MD 25.40 (8 studies; N=644; 95%CI 16.25 to 34.54, I² 68%); at 6 months MD 35.75 (4 studies; N=455; 95%CI 22.23 to 49.27, I² 74%) ▪ Meditative movement vs walking exercise: at 3 months MD 15.53 (2 studies; N=224; 95%CI 11.59 to 19.48, I² 0%); at 6 months MD 19.36 (4 studies; N=430; 95%CI 9.0 to 29.72, I² 83%)	

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Kaminsky 2017	• Design: RCT (NCT01633697)	• Eligibility criteria: adult patients diagnosed with COPD with	Pranayama breathing with education (N=21)	CRITICAL OUTCOMES • Dyspnoea:	Level of evidence: high risk of bias

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Funding: National Institutes of Health, NHLBI R34 HL113290 CoI: authors declared no competing financial interests • Setting: two academic pulmonary practices, US • Sample size: N=43 • Duration: 12 weeks, Jan 2013 - Oct 2015	symptoms of shortness of breath, mMRC Dyspnea Scale score >2 and FEV_1/forced <0.7, FEV_1<80%, current non-smokers with no enrolment in PR or other yoga practising • *A priori* patient characteristics: ○ Mean age: 68y ○ Men: 61% ○ FEV_1: 42.5%	vs. Education alone (N=22)	○ mMRC at 12w: 2.1 vs. 2.4 (group x time p=0.21) ○ BDI/TDI at 12w: 0.89 vs. -0.05 ○ CAT at 12w: 17.7 vs. 17.5 (group x time p=0.31) ○ Borg-score at 12w: 2.18 vs. 2.50 (group x time p=0.32) • Quality of life ○ SGRQ at 12w: 42.2 vs. 49.8 (group x time p=0.39) IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: ○ 6MWD at 12w: 316 vs. 252m; increase in intervention group 28 m (95%CI -5 to 61) vs. control -15 m (95%CI -47 to 16), p=0.06 (group x time) ○ Difference in 6MWD at 12 weeks: 65m (95%CI 2 to 129, p=0.04)	• Computer-generated randomization scheme administered by the statistician • Different set of research coordinators who were blinded to group assignment conducted all measurements and assessments • 3 drop-outs excluded from analysis

GRADE profielen

Active mind-body movement therapy vs. pulmonary rehabilitation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AMBMT	PR	Relative (95%CI)	Absolute		
Dyspnoea: mMRC												
2	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	62	65	MD 0.00 -0.37 to 0.37	-	VERY LOW	CRITICAL
Dyspnoea: Borg-scale												
1	RCT	Very serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	70	69	MD -0.44 -0.88 to 0.00	-	VERY LOW	CRITICAL

Dyspnoea: CRQ dyspnoea subscale												
1	RCT	Serious[5]	No serious inconsistency	No serious indirectness	Very serious[6]	None	8	3	MD -0.21 -2.81 to 2.38	-	VERY LOW	CRITICAL
Quality of life: SGRQ total score												
3	RCT	Serious[7]	No serious inconsistency	No serious indirectness	Serious[8]	None	124	125	MD -5.83 -8.75 to -2.92	-	LOW	CRITICAL
Quality of life: CAT												
1	RCT	Very serious[9]	No serious inconsistency	No serious indirectness	No serious imprecision	None	36	38	MD -6.58 -9.16 to -4.00	-	LOW	CRITICAL
Exercise tolerance: incremental cyclo-ergometry												
1	RCT	Very serious[10]	No serious inconsistency	No serious indirectness	Serious[11]	None	18	18	MD 55 -157.82 to 267.82	-	VERY LOW	IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: unclear allocation concealment, no blinding of patients and clinicians, unclear ITT analysis.

[2] Estimated SMD = 0.01 (95%CI -0.58 to 0.59); CI includes -0.5 and 0.5.

[3] High risk of bias: unclear allocation concealment, no blinding, no ITT analysis.

[4] Estimated SMD = -0.33 (95%CI -0.67 to 0.00); CI includes -0.5.

[5] High risk of bias: no blinding.

[6] Estimated SMD = -0.15 (95%CI -1.48 to 1.18); CI includes -0.5 and 0.5.

[7] High risk of bias: unclear allocation concealment, no blinding of patients and clinicians, unclear or no ITT analysis.

[8] Estimated SMD = -0.47 (95%CI -0.79 to -0.15); CI includes -0.5.

[9] High risk of bias: unclear allocation concealment, no blinding, unclear ITT analysis.

[10] High risk of bias: unclear allocation concealment, no blinding, unclear ITT analysis.

[11] Estimated SMD = 0.17 (95%CI -0.49 to 0.82); CI includes 0.5.

Active mind-body movement therapy + pulmonary rehabilitation vs. pulmonary rehabilitation alone

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**AMBMT + PR**	**PR**	**Relative (95%CI)**	**Absolute**		
Dyspnoea: CRQ dyspnoea subscale												

1	RCT	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	40	40	MD 0.04 -2.18 to 2.26	-	LOW	CRITICAL
Dyspnoea: Borg-scale												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	94	98	MD -0.10 -0.37 to 0.17	-	LOW	CRITICAL
Quality of life: SGRQ total score												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	94	98	MD -2.57 -7.76 to 2.62	-	LOW	CRITICAL
Quality of life: SF-36 general health												
1	RCT	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	40	40	MD 5.42 3.82 to 7.02	-	LOW	CRITICAL
Quality of life: SF-36 mental health												
1	RCT	Very serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	40	40	MD 3.20 1.45 to 4.95	-	VERY LOW	CRITICAL
Exercise tolerance: 6MWD												
2	RCT	Very serious[4]	No serious inconsistency	No serious indirectness	No serious imprecision	None	134	138	MD 14.09 -3.68 to 31.86	-	LOW	IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: no blinding, no ITT analysis.

[2] High risk of bias: no allocation concealment, no blinding, no ITT analysis.

[3] Estimated SMD = 0.79 (95%CI 0.34 to 1.25); CI includes 0.5.

[4] High risk of bias: no allocation concealment (1 study), no blinding or ITT analysis (2 studies).

Tai Chi vs. usual care

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tai Chi**	**Usual care**	**Relative (95%CI)**	**Absolute**		
Dyspnoea: Borg-scale												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	70	67	MD -0.2 -0.67 to 0.27	-	LOW	CRITICAL

Dyspnoea: UCSD SOB Questionnaire											
1	RCT	Very serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	None	5	5	MD 5 -11.62 to 21.62	-	VERY LOW	CRITICAL
Dyspnoea: mMRC											
2	RCT	Very serious[4]	No serious inconsistency	No serious indirectness	Serious[5]	None	47	49	MD -0.15 -0.56 to 0.26	-	VERY LOW	CRITICAL
Dyspnoea: CRQ dyspnoea subscale											
2	RCT	Serious[6]	Serious[18]	No serious indirectness	Very serious[7]	None	24	24	MD 0.05 -1.32 to 1.42	-	VERY LOW	CRITICAL
Quality of life: SGRQ total score											
3	RCT	Very serious[1,4]	Serious[8]	No serious indirectness	Serious[9]	None	117	116	MD -7.85 -16.53 to 0.83	-	VERY LOW	CRITICAL
Quality of life: CRQ total score											
2	RCT	Serious[6]	No serious inconsistency	No serious indirectness	Serious[10]	None	24	24	MD 0.41 -0.54 to 1.35	-	LOW	CRITICAL
Exercise tolerance: 6MWD											
6	RCT	Very serious[11]	No serious inconsistency	No serious indirectness	Serious[12]	None	160	158	MD 29.64 10.52 to 48.77	-	VERY LOW	IMPORTANT
Exercise tolerance: ISWT											
1	RCT	Serious[13]	No serious inconsistency	No serious indirectness	Very serious[14]	None	19	19	MD 2 -95.26 to 99.26	-	VERY LOW	IMPORTANT
Exercise tolerance: ESWT											
1	RCT	Serious[13]	No serious inconsistency	No serious indirectness	Serious[15]	None	19	19	MD 373 135.72 to 610.58	-	VERY LOW	IMPORTANT
Exercise tolerance: exercise duration											
1	RCT	Very serious[2]	No serious inconsistency	No serious indirectness	Very serious[16]	None	5	5	MD 1 -1.1 to 3.1	-	VERY LOW	IMPORTANT
Exercise tolerance: Peak VO_2 uptake											

1	RCT	Very serious[2]	No serious inconsistency	No serious indirectness	Very serious[17]	None	5	5	MD -2 -5.76 to 1.76	-	VERY LOW	IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: unclear allocation concealment, no blinding of patients and clinicians, no ITT analysis.

[2] High risk of bias: unclear allocation concealment, no blinding of patients and clinicians.

[3] Estimated SMD = 0.34 (95%CI -0.92 to 1.59); CI includes -0.5 and 0.5.

[4] High risk of bias: unclear randomization (1 study) and allocation concealment (2 studies), no blinding of patients and clinicians (2 studies), unclear ITT analysis (2 studies).

[5] Estimated SMD = -0.13 (95%CI -0.52 to 0.26); CI includes -0.5.

[6] High risk of bias: unclear allocation concealment (1 study), no blinding of patients and clinicians (2 studies).

[7] Estimated SMD = 0.07 (95%CI -1.36 to 1.49); CI includes -0.5 and 0.5.

[8] I^2 85%, non-overlapping CI.

[9] Estimated SMD = -0.66 (95%CI -1.44 to 0.12); CI includes -0.5.

[10] Estimated SMD = 0.43 (95%CI -0.15 to 1.00); CI includes 0.5.

[11] High risk of bias: unclear allocation concealment (5 studies), no blinding of patients and clinicians (6 studies), no unclear ITT analysis (4 studies).

[12] Estimated SMD = 0.66 (95%CI 0.43 to 0.89); CI includes - 0.5.

[13] High risk of bias: no blinding of patients and clinicians.

[14] Estimated SMD = 0.01 (95%CI -0.62 to 0.65); CI includes -0.5 and 0.5.

[15] Estimated SMD = 0.98 (95%CI 0.30 to 1.65); CI includes 0.5.

[16] Estimated SMD = 0.54 (95%CI -0.74 to 1.81); CI includes -0.5 and 0.5.

[17] Estimated SMD = -0.59 (95%CI -1.87 to 0.69); CI includes -0.5 and 0.5.

[18] I^2 85%.

Tai Chi + breathing exercise vs. breathing exercise

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tai Chi + BE**	**BE**	**Relative (95%CI)**	**Absolute**		
Dyspnoea: Borg-scale												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	40	40	MD -1.3 -2.02 to -0.58	-	VERY LOW	CRITICAL
Quality of life: SGRQ total score												
2	RCT	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	60	60	MD -1.32 -5.92 to 3.28	-	LOW	CRITICAL

Exercise tolerance: 6MWD											
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	30	30	MD 22 -6 to 50	-	VERY LOW	IMPORTANT
Physical functioning											
0	No evidence											IMPORTANT

[1] High risk of bias: unclear randomization and allocation concealment, no blinding of patients and clinicians, unclear ITT analysis.

[2] Estimated SMD = -0.78 (95%CI -1.24 to -0.33); CI includes -0.5.

[3] High risk of bias: unclear randomization (1 study) and allocation concealment (2 studies), no blinding of patients and clinicians (2 studies), unclear ITT analysis (2 studies).

[4] Estimated SMD = 0.39 (95%CI -0.12 to 0.90); CI includes 0.5.

Tai Chi + exercise vs. exercise

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tai Chi + exercise**	**Exercise**	**Relative (95%CI)**	**Absolute**		
Dyspnoea												
0	No evidence											CRITICAL
Quality of life: SGRQ total score												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	98	94	MD -3.76 -8.72 to 1.2	-	MODERATE	CRITICAL
Exercise tolerance: 6MWD												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	98	94	MD 1.5 -18.76 to 21.76	-	MODERATE	IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: no blinding.

Meditative movement vs. non-exercise

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MM**	**Usual care**	**Relative (95%CI)**	**Absolute**		

Dyspnoea: CRQ dyspnoea at 3 months											
2	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	24	24	MD 0.9 0.51 to 1.29	-	LOW	CRITICAL
Quality of life: CRQ total score at 3 months											
2	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	24	24	MD 1.92 0.54 to 3.31	-	VERY LOW	CRITICAL
Quality of life: CRQ mastery at 3 months											
2	RCT	Serious[1]	Serious[4]	No serious indirectness	Very serious[5]	None	24	24	MD 1.57 -0.49 to 3.62	-	VERY LOW	CRITICAL
Exercise tolerance: 6MWD at 3 months											
8	RCT	Serious[6]	No serious inconsistency	No serious indirectness	Serious[7]	None	309	335	MD 25.40 16.25 to 34.54	-	LOW	IMPORTANT
Exercise tolerance: 6MWD at 6 months											
4	RCT	Serious[8]	No serious inconsistency	No serious indirectness	Serious[9]	None	226	229	MD 35.75 22.23 to 49.27	-	LOW	IMPORTANT
Physical functioning											
0	No evidence											IMPORTANT

[1] High risk of bias: no blinding of patients and clinicians (see Ngai 2016).

[2] Estimated SMD = 1.22 (95%CI 0.00 to 2.44); CI includes 0.5.

[3] Estimated SMD = 3.44 (95%CI -3.63 to 10.52); CI includes -0.5 and 0.5.

[4] I^2 96%.

[5] Estimated SMD = 2.90 (95%CI -2.46 to 8.26); CI includes -0.5 and 0.5.

[6] High risk of bias: unclear randomization (4 studies), unclear allocation concealment (6 studies), unclear blinding (2 studies), unclear ITT analysis (3 studies).

[7] Estimated SMD = 1.05 (95%CI 0.43 to 1.68); CI includes 0.5.

[8] High risk of bias: unclear randomization (1 study), unclear allocation concealment (3 studies), unclear blinding (2 studies), unclear ITT analysis (1 study).

[9] Estimated SMD = 1.61 (95%CI 0.35 to 2.86); CI includes 0.5.

Meditative movement vs. walking exercise

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MM	Walking exercise	Relative (95%CI)	Absolute		
Dyspnoea: CRQ dyspnoea at 6 months												
2	RCT	Serious[1]	Serious[2]	No serious indirectness	Very serious[2]	3None	103	103	MD 0.46 -0.28 to 1.20	-	VERY LOW	CRITICAL
Quality of life: CRQ mastery												
2	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	103	103	MD 0.0 -0.32 to 0.33	-	VERY LOW	CRITICAL
Exercise tolerance: 6MWD at 3 months												
2	RCT	Serious[5]	No serious inconsistency	No serious indirectness	Serious[6]	None	112	112	MD 15.53 11.59 to 19.48	-	LOW	IMPORTANT
Exercise tolerance: 6MWD at 6 months												
4	RCT	Serious[7]	Serious[8]	No serious indirectness	Serious[9]	None	215	215	MD 19.36 9.00 to 29.72	-	VERY LOW	IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

Yoga (Pranayama) breathing

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga + education	Education	Relative (95%CI)	Absolute		
Dyspnoea: mMRC at 12 w												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	21	22	-	2.1 vs. 2.4 (p=0.21)	LOW	CRITICAL
Dyspnoea: BDI/TDI at 12 w												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	21	22	-	0.89 vs. -0.05	LOW	CRITICAL
Dyspnoea: CAT at 12 w												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	21	22	-	17.7 vs. 17.5 (p=0.31)	VERY LOW	CRITICAL

Dyspnoea: Borg-score at 12 w												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[5]	None	17	22	-	2.18 vs. 2.50 (p=0.32)	LOW	CRITICAL
Quality of life: SGRQ at 12 w												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[6]	None	21	22	-	42.2 vs. 49.8 (p=0.39)	LOW	CRITICAL
Exercise tolerance: 6MWD at 12 w												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[7]	None	21	22	MD 65 2 to 129	-	LOW	IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: unclear allocation concealment, unclear blinding of patients and clinicians, no ITT analysis (3 dropouts).

[2] Estimated SMD = -0.31 (95%CI -0.91 to 0.29); CI includes -0.5.

[3] Estimated SMD = 0.45 (95%CI -0.15 to 1.06); CI includes 0.5.

[4] Estimated SMD = 0.03 (95%CI –0.57 to 0.63); CI includes -0.5 and 0.5.

[5] Estimated SMD = -0.17 (95%CI -0.80 to 0.47); CI includes -0.5.

[6] Estimated SMD = -0.43 (95%CI -1.03 to 0.18); CI includes -0.5.

[7] Estimated SMD = 0.57 (95%CI -0.04 to 1.18); CI includes 0.5.

c. Hulpmiddelen bij het lopen

Evidence tabel

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Lee 2018	• Design: systematic review, PROSPERO CRD42016041397 • Funding: not reported; CoI: declared having no CoI • Search date: Aug 2016	• Eligibility criteria: patients with COPD (physician-based and/or lung function), stable state or acute exacerbation • *A priori* patient characteristics: ○ Mean age: 63-72 years ○ Male: 42-100%	Use of rollator with a frame vs. Control (no aid)	CRITICAL OUTCOMES • Dyspnoea: ○ End-6MWT Borg dyspnoea score: MD 0.97 (95%CI 0.63 to 1.32, 3 studies) • Quality of life: Chronic Respiratory Disease Questionnaire ○ Dyspnoea: MD 0.35 (95%CI -0.04 to 0.74, p=0.08)	Level of evidence: high risk of bias • Review process in duplicate • Unclear if language restrictions

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Databases: MEDLINE, CINAHL, PEDro, PubMed, EMBASE, and the Cochrane Library databases • Study designs: RCTs and randomized cross-over trials • N included studies: N=7			○ Fatigue: MD 0.43 (95%CI 0.02 to 0.84, p=0.04) ○ Emotional function: MD 0.14 (95%CI -0.21 to 0.48, p=0.44) ○ Mastery: MD 0.19 (95%CI -0.07 to 0.44, p=0.16) IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: ○ 6-MWD: MD 13 m (95%CI 5 to 22, 3 studies) 12-MWD: 434.6 vs. 388.3 m, p>0.05 (1 study)	

GRADE profielen

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rollator	No rollator	Relative (95%CI)	Absolute		
Dyspnoea: end-6MWD Borg dyspnoea score												
3	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	82	82	MD 0.97 0.63 to 1.32	-	LOW	CRITICAL
Quality of life: Chronic Respiratory Disease Questionnaire – dyspnoea												
2	RCT	Serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	?	?	MD 0.35 -0.04 to 0.74	-	LOW	CRITICAL
Quality of life: Chronic Respiratory Disease Questionnaire – fatigue												
2	RCT	Serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	?	?	MD 0.43 0.02 to 0.84	-	LOW	CRITICAL
Quality of life: Chronic Respiratory Disease Questionnaire – emotional function												
2	RCT	Serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	?	?	MD 0.14 -0.21 to 0.48	-	LOW	CRITICAL
Quality of life: Chronic Respiratory Disease Questionnaire – mastery												

2	RCT	Serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	?	?	MD 0.19 -0.07 to 0.44	-	LOW	CRITICAL
Exercise tolerance: 6MWD												
3	RCT	Serious[1]	Serious[5]	No serious indirectness	Serious[2]	None	82	82	MD 13.44 4.98 to 21.90	-	VERY LOW	IMPORTANT
Exercise tolerance: 12MWD												
1	RCT	Serious[6]	No serious inconsistency	No serious indirectness	Serious[7]	None	12	12	-	434.6 vs. 388.3 m, p>0.05	LOW	IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: unclear randomization and allocation concealment, absent or unclear blinding.

[2] Total sample size = 82 (x2 because cross-over); rule of thumb = 400.

[3] High risk of bias: unclear randomization (1 study) and allocation concealment (2 studies), absent or unclear blinding (2 studies).

[4] Total sample size = 50; rule of thumb = 400.

[5] I^2 75%.

[6] High risk of bias: unclear randomization and allocation concealment, absent blinding.

[7] Total sample size = 12 (x2 because cross-over); rule of thumb = 400.

d. Ventilator

Evidence tabel

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Qian 2019	• Design: systematic review • Funding: no funding received; CoI: declared having no CoI • Search date: Sep 2018 • Databases: Medline, EMBASE, Web of Science, Scopus, CINAHL, PsycInfo,	• Eligibility criteria: adult patients with dyspnoea • *A priori* patient characteristics: ○ Mean age: 62-75 years ○ COPD: 43%	Handheld or electric fan	CRITICAL OUTCOMES • Dyspnoea: ○ Bausewein 2010 (64% COPD): fan vs. placebo wristband: -0.6 vs. -0.8; p=0.9 ○ Galbraith 2010 (52% COPD): fan to face vs. fan to leg: -7 vs. -1.5; p=0.003 ○ Johnson 2016 (47% COPD): fan vs. no intervention: -6 vs. -5; p=0.853	Level of evidence: high risk of bias • Review process in duplicate • Language restriction: Chinese, English

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Cochrane Library, clinicaltrials.gov, ICTRP, Central • Study designs: RCTs, cohort studies • N included studies: N=10, of which 9 RCTs (344 patients); 6 RCTs with COPD			○ Kako 2018 (22% COPD): no fan vs. fan to leg vs. fan to face: 0 vs. 0 vs. -0.7; p=0.02 ○ Marchetti 2015 (100% COPD): fan to face vs. fan to leg: 5 vs. 6.5; p=0.03 ○ O'Driscoll 2011 (100% COPD): room air vs. electric fan vs. air mask vs. oxygen mask: 5.1 vs. 5.1 vs. 5.3 vs. 5.1 • Quality of life: not reported IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: not reported	

GRADE profielen

Handheld or electric fan

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fan	No fan	Relative (95%CI)	Absolute		
Dyspnoea												
3	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	?	?	-	See evidence tables	VERY LOW	CRITICAL
Quality of life												
0	No evidence											CRITICAL
Exercise tolerance												
0	No evidence											IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: unclear allocation concealment (1/3), no blinding (3/3).

[2] Insufficient information to assess precision.

Fan to the face vs. fan to the leg

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fan face**	**Fan leg**	**Relative (95%CI)**	**Absolute**		
Dyspnoea												
3	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	?	?	-	See evidence tables	VERY LOW	CRITICAL
Quality of life												
0	No evidence											CRITICAL
Exercise tolerance												
0	No evidence											IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: no blinding (3/3).

[2] Insufficient information to assess precision.

e. Breathlessness support services

Evidence tabellen

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Farquhar 2016	• Design: RCT (ISRCTN04119516, NCT00678405) • Funding: NIHR; CoI: authors declared different funding support from Macmillan Cancer Support, Cicely Saunders	• Eligibility criteria: patients with non-malignant conditions and a diagnosed cause of breathlessness, troubled by breathlessness in spite of optimisation of underlying illness, and possible benefit from a self-management programme, no previous BIS	The Breathlessness Intervention Service (BIS; N=44): - Thorough psychological and physical assessment taking into account patient and carer needs	CRITICAL OUTCOMES • Dyspnoea: o NRS distress due to breathlessness (0-10): MD at 4w adjusted for baseline = -0.24 (95%CI -1.30 to 0.82; p=0.65) • Quality of life: o CRQ mastery: MD at 4w adjusted for baseline = 0.43 (95%CI -0.02 to 0.89; p=0.06)	Level of evidence: high risk of bias • Randomly permuted blocks of random size 2, 4 and 6, generated by the study statistician and concealed within sealed opaque envelopes until allocation

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	International, the Gatesby Foundation • Setting: Cambridge, UK • Sample size: N=87 • Duration: Jul 2008 –Jun 2010	• *A priori* patient characteristics: ○ Mean age: 72 years ○ Men: 61 % ○ COPD: 83% ○ COPD-classification: moderate 20%; severe 42%; very severe 33% ○ CRQ dyspnoea score: 3.09	and breathlessness triggers - Treatment plan is agreed and implemented incorporating a range of evidence-based non-pharmacological and pharmacological techniques relevant to the patient and their lifestyle, helping them to self-manage their symptoms - Personal emergency plan is agreed and practised, with each patient receiving a copy - Paper copies of quality controlled information leaflets are provided vs. Standard care (N=43)	IMPORTANT OUTCOMES • Physical functioning: not reported ○ Exercise tolerance: not reported	notification by the intervention deliverer • Patients aware of allocation • Researchers were blinded (but not guaranteed) • Not completely clear if ITT analysis was used • Not all outcomes mentioned in the protocol are reported in the main article
Higginson 2014	• Design: RCT (NCT01165034) • Funding: NIHR; CoI: declared no CoI • Setting: 3 teaching hospitals, South London, mainly outpatient • Sample size: N=105 • Duration: Oct 2010 - Sep 2012	• Eligibility criteria: adults with refractory breathlessness on exertion or rest (MRC dyspnoea scale score ≥2); advanced disease such as cancer, COPD, chronic heart failure, interstitial lung disease, and motor neuron disease • Exclusion: breathlessness of unknown cause; primary	Breathlessness support service (N=53): - First outpatient clinic appointment with respiratory medicine and palliative care clinicians assessing present treatment and concerns - The patient (and family if present) is given a	CRITICAL OUTCOMES • Dyspnoea: ○ NRS breathlessness average 24h: MD -0.33 (95%CI -1.28 to 0.62, p=0.49) ○ NRS breathlessness worst at rest 24h: MD -0.35 (-1.71 to 1.01, p=0.61) ○ NRS breathlessness on exertion 24h: MD -0.73 (95%CI -1.69 to 0.22, p=0.13) ○ CRQ dyspnoea: MD 0.08 (95%CI -0.38 to 0.52, p=0.75)	Level of evidence: high risk of bias • Online randomisation system, independent of research and clinical teams • Adequate allocation concealment • Patients aware of allocation

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		diagnosis of chronic hyperventilation syndrome; completely house (or hospital or nursing home) bound, despite offer of free transport to clinic; or within 2 weeks of treatment for an acute exacerbation • *A priori* patient characteristics: ○ Mean age: 67 years ○ Men: 58% ○ COPD: 54% ○ Cancer: 20% ○ Interstitial lung disease: 18% ○ Predicted FEV_1: 46.2% ○ CRQ dyspnoea score: 2.2	breathlessness pack including information, management, and pacing guidance, a hand-held fan or water spray, and a poem (a short mantra to help breathing and relaxation during crises) and helped to agree a crisis plan - A home assessment is done 2–3 weeks after the clinic visit by a physiotherapist and/or occupational therapist to assess the need for walking and home aids and adaptations, reinforcement of self-management, and further guidance on pacing and exercises, including a DVD when appropriate - 4 weeks after the first clinic visit, a second and final clinic appointment with a palliative care specialist is arranged to agree further actions and a discharge plan vs.	• Quality of life: ○ CRQ mastery: MD 0.58 (95%CI 0.01 to 1.15, p=0.048, effect size=0.44) ○ CRQ HRQL: MD 4.21 (95%CI -4.52 to 12.94, p=0.34) ○ EQ-5D index: MD 0.092 (95%CI -0.23 to 0.04; p=0.18) ○ EQ-5D HRQL VAS: MD 1 (95%CI -6.67 to 10.34; p=0.67) IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: not reported	• Researchers were blinded (but not guaranteed) • No ITT analysis • Outcomes measured at 6w

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
			Usual care (N=52)		

GRADE profielen

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BSS	Usual care	Relative (95%CI)	Absolute		
Dyspnoea: NRS distress due to breathlessness												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	44	43	MD -0.24 -0.02 to 0.89	-	LOW	CRITICAL
Dyspnoea: NRS breathlessness average 24h												
1	RCT	Serious[3]	No serious inconsistency	Serious[4]	Serious[5]	None	42	40	MD -0.33 -1.28 to 0.62	-	VERY LOW	CRITICAL
Dyspnoea: NRS breathlessness worst at rest 24h												
1	RCT	Serious[3]	No serious inconsistency	Serious[4]	Serious[5]	None	42	40	MD -0.35 -1.71 to 1.01	-	VERY LOW	CRITICAL
Dyspnoea: NRS breathlessness on exertion 24h												
1	RCT	Serious[3]	No serious inconsistency	Serious[4]	Serious[5]	None	42	40	MD -0.73 -1.69 to 0.22	-	VERY LOW	CRITICAL
Dyspnoea: CRQ dyspnoea												
1	RCT	Serious[3]	No serious inconsistency	Serious[4]	Serious[5]	None	42	40	MD 0.08 -0.38 to 0.52	-	VERY LOW	CRITICAL
Quality of life: CRQ mastery												
2	RCT	Serious[1, 3]	No serious inconsistency	No serious indirectness	Serious[6]	None	44	43	MD 0.43 -0.02 to 0.89	-	LOW	CRITICAL
							42	40	MD 0.58 0.01 to 1.15	-		
Quality of life: CRQ HRQL												
1	RCT	Serious[3]	No serious inconsistency	Serious[4]	Serious[5]	None	42	40	MD 4.21 -4.52 to 12.94	-	VERY LOW	CRITICAL

Quality of life: EQ-5D												
1	RCT	Serious[3]	No serious inconsistency	Serious[4]	Serious[5]	None	42	40	MD 0.092 -0.23 to 0.04	-	VERY LOW	CRITICAL
Exercise tolerance												
0	No evidence											IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: unclear randomization, no blinding of patients.

[2] Total sample size = 87; rule of thumb = 400; optimal information size not reached.

[3] High risk of bias: no blinding of patients, no ITT analysis.

[4] 46% of patients had no COPD.

[5] Total sample size = 82; rule of thumb = 400; optimal information size not reached.

[6] Total sample size = 169; rule of thumb = 400.

f. Zuurstof

Evidence tabellen

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Ameer 2014	• Design: systematic review • Funding: Respiratory Medicine Unit; The Queen Elizabeth Hospital, Australia; CoI: authors declared none • Search date: Nov 2012 • Databases: Cochrane Airways Group Specialised Register, MEDLINE, EMBASE CINAHL, Controlled Clinical Trials, government registries, WHO registries	• Eligibility criteria: adult patients with stable COPD, with chronic hypoxaemia (resting PaO2: 55-69 mmHg) without cor pulmonale, or PaO2 ≥ 60 mmHg, or hypoxaemia on activity (PaO2 < 60 mmHg or peripheral capillary oxygen de-saturation to < 88% SpO2) with or without cor pulmonale with symptoms on exertion • *A priori* patient characteristics: ○ Mean age: 71 years	Long-term ambulatory oxygen therapy provided through portable oxygen cylinders or with the use of liquid oxygen canisters or battery-powered portable oxygen concentrators	CRITICAL OUTCOMES • Dyspnoea: ○ Ambulatory oxygen therapy versus placebo (air): ▪ Borg-score during 6MWD: MD -0.60 (95%CI -1.39 to 0.19) ▪ Borg-score during step exercise test: MD -0.60 (95%CI -1.28 to 0.08) ▪ CRQ dyspnoea: MD 0.28 (4 studies; 95%CI 0.10 to 0.45; I^2 0%) ▪ Acute post-6MWD dyspnoea score: cylinder oxygen 4.1 ± 1.8; cylinder air 4.8 ± 1.5; p=0.005	Level of evidence: high risk of bias • Review process in duplicate • Included studies: McDonald 1995, Eaton 2002, Moore 2011, Nonoyama 2007

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Study designs: RCTs • N included studies: N=4 (331 patients)			▪ Post-5MWD dyspnoea score: MD -0.44 (95%CI -0.86 to -0.02) • Quality of life: ○ Ambulatory oxygen therapy versus placebo (air): ▪ CRQ mastery: MD 0.13 (4 studies; 95%CI -0.06 to 0.3; I^2 48%) IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: ○ Ambulatory oxygen therapy vs. air: 6MWD ▪ Cylinder air: OR 1.05 (2 studies; 95%CI 0.62-1.75; I^2 0%); MD 1.19 (95%CI 0.80-1.77) ▪ Cylinder oxygen: MD 1.27 (1 study; 95%CI 0.48-3.39)	
Ekström 2016	• Design: systematic review • Funding: Heart-Lung foundation, Wera and Emil Cornell Foundation, The Swedish Society of Medicine, The Scientific Committee of Blekinge County Council; CoI: one author has relations to pharmaceutical manufacturers and FDA • Search date: Jul 2016 • Databases: Cochrane Airways Group Register, CENTRAL, MEDLINE andb Embase,	• Eligibility criteria: patients 18 years or older with COPD, with mild or no hypoxaemia (mean PaO2 > 7.3 kPa) and did not qualify for home oxygen therapy • *A priori* patient characteristics: ○ Baseline PaO2 was provided in 30 of 44 studies, ranging from 7.7 to 11.3 kPa	Oxygen delivered through a non-invasive method	CRITICAL OUTCOMES • Dyspnoea: ○ All trials: SMD -0.31 (95%CI -0.43 to -0.20; I^2 29%) ○ Trials using short-burst oxygen: SMD -0.03 (95%CI -0.28 to 0.22; 4 studies; I^2 0%) ○ Trials not using short-burst oxygen: SMD -0.36 (95%CI -0.48 to -0.24; 28 studies; I^2 = 27%) ○ Trials with desaturation during exercise: SMD -0.28 (95%CI -0.39 to -0.16; 16 studies) ○ Trials without exertional desaturation: SMD -0.47 (95%CI -0.69 to -0.24; 15 studies) • Quality of life: SMD 0.12 (95%CI -0.04 to 0.28; 5 studies; I^2 0%)	Level of evidence: high risk of bias • Review process in duplicate

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	ClinicalTrials.gov, WHO trials portal • Study designs: RCTs • N included studies: N=44 (1195 patients)			IMPORTANT OUTCOMES • Physical functioning: not reported • Exercise tolerance: not reported	

Abbreviations: 95%CI: 95% confidence interval; 12MWD: 12-minutes walking distance; 6MWD: 6-minutes walking distance; AMBMT: active mind body movement therapy; BCSS: breathlessness, cough and sputum scale; BDI/TDI: Baseline and Transition Dyspnea Indexes; BIPAP: Bilevel Positive Airway Pressure; CAT: COPD assessment tool; CCT: controlled clinical trial; CoI: conflicts of interest; COPD: chronic obstructive pulmonary disease; CPET: cardiopulmonary exercise testing; CRQ: chronic respiratory questionnaire; CWRT: constant work rate test; EMT: expiratory muscle training; EQ-5D: EuroQol Five Dimensions; ESWT: endurance shuttle walk test; ET: exercise training; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GP: general practitioner; GOLD: Global Initiative for Chronic Obstructive Lung Disease; GRC: global rating of change; HFCWO: High-frequency chest wall oscillation; IMT: inspiratory muscle training; IPPB: intermittent positive pressure breathing; IPV: intrapulmonary percussive ventilation; ISWT: incremental shuttle walk test; ITT: intention-to-treat; MD: mean difference; LTOT: long-term oxygen therapy; MRC: Medical Research Council; mMRC: modified Medical Research Council; MRF-28: Maugeri Foundation Respiratory Failure Questionnaire; NIPPV: non-invasive positive pressure ventilation; NIV: non-invasive ventilation; NRS: numeric rating scale; PLB: pursed lip breathing; PR: pulmonary rehabilitation; QOL: quality of life; RCT: randomized controlled trial; SD: standard deviation; SGRQ: Saint George Respiratory Questionnaire; SMD: standardized mean difference; SRI: severe respiratory insufficiency questionnaire; TPEP: temporary positive expiratory pressure; UCSD SOB: University of California, San Diego Shortness of Breath Questionnaire; VAS: visual analogue scale; VO2: volume zuurstof; WMD: weighted mean difference.

GRADE profielen

LTOT in COPD patients without hypoxaemia at rest

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxygen	Air	Relative (95%CI)	Absolute		
Dyspnoea: Borg-score during 6MWD												
1	RCT	No serious ROB	No serious inconsistency	No serious indirectness	Serious[1]	None	26	26	MD -0.60 -1.39 to 0.19	-	MODERATE	CRITICAL
Dyspnoea: Borg-score during step exercise test												
1	RCT	No serious ROB	No serious inconsistency	No serious indirectness	Serious[2]	None	26	26	MD -0.60 -1.28 to 0.08	-	MODERATE	CRITICAL
Dyspnoea: CRQ dyspnoea												
4	RCT	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision[4]	None	?	?	MD 0.28 0.10 to 0.45	-	MODERATE	CRITICAL
Dyspnoea: acute post-6MWD dyspnoea score												

1	RCT	Very serious[5]	No serious inconsistency	No serious indirectness	Serious[6]	None	39	39	Cylinder oxygen 4.1 ± 1.8; cylinder air 4.8 ± 1.5; p=0.005	-	VERY LOW	CRITICAL
Dyspnoea: Post-6MWD dyspnoea score												
1	RCT	Very serious[5]	No serious inconsistency	No serious indirectness	Serious[7]	None	27	27	MD -0.44 -0.86 to -0.02	-	VERY LOW	CRITICAL
Quality of life: CRQ mastery												
CRQ mastery	**CRQ mastery**	**CRQ mastery**	**CRQ mastery**	**CRQ mastery**	**CRQ mastery**	**CRQ mastery**	**CRQ mastery**	**CRQ mastery**	**CRQ mastery**	**CRQ mastery**	**CRQ mastery**	**CRQ mastery**
Exercise tolerance: 6MWD cylinder air												
2	RCT	No serious ROB	No serious inconsistency	No serious indirectness	Serious[7]	None	94	101	MD 1.19 0.80 to 1.77	-	MODERATE	IMPORTANT
Exercise tolerance: 6MWD cylinder oxygen												
1	RCT	No serious ROB	No serious inconsistency	No serious indirectness	Serious[7]	None	26	26	MD 1.27 0.48 to 3.39	-	MODERATE	IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] Estimated SMD = -0.41 (95%CI -0.96 to 0.14); CI includes -0.5.

[2] Estimated SMD = -0.47 (95%CI -1.02 to 0.08); CI includes -0.5.

[3] High risk of bias: unclear randomization, allocation concealment and ITT analysis in 2/4 studies.

[4] CI around MD does not cross the MID of 0.5.

[5] High risk of bias: unclear randomization, allocation concealment and ITT analysis.

[6] Estimated SMD = -0.42 (95%CI -0.87 to 0.03); CI includes -0.5.

[7] Insufficient information to estimate precision; rule of thumb of 400 participants not reached.

Oxygen in COPD patients with mild or no hypoxaemia

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oxygen**	**Air**	**Relative (95%CI)**	**Absolute**		
Dyspnoea (all instruments): all studies												

32	RCT	No serious ROB[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	?	?	SMD -0.31 -0.43 to -0.20	-	HIGH	CRITICAL
Dyspnoea (all instruments): studies using short-burst oxygen												
4	RCT	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	?	?	SMD -0.03 -0.28 to 0.22	-	MODERATE	CRITICAL
Dyspnoea (all instruments): studies not using short-burst oxygen												
28	RCT	No serious ROB[3]	No serious inconsistency	No serious indirectness	No serious imprecision	None	?	?	SMD 0.36 - 0.48 to -0.24	-	HIGH	CRITICAL
Dyspnoea (all instruments): studies with exertional desaturation												
16	RCT	Serious[4]	No serious inconsistency	No serious indirectness	No serious imprecision	None	?	?	SMD -0.28 -0.39 to -0.16	-	MODERATE	CRITICAL
Dyspnoea (all instruments): studies without exertional desaturation												
15	RCT	Serious[5]	No serious inconsistency	No serious indirectness	Serious[6]	None	?	?	SMD -0.47 -0.69 to -0.24	-	LOW	CRITICAL
Quality of life												
5	RCT	Serious[7]	No serious inconsistency	No serious indirectness	No serious imprecision	None	?	?	SMD 0.12 -0.04 to 0.28	-	MODERATE	CRITICAL
Exercise tolerance												
0	No evidence											IMPORTANT
Physical functioning												
0	No evidence											IMPORTANT

[1] Exclusion of 7 trials with high risk of bias keeps result +/- unchanged (SMD -0.30, 95%CI -0.41 to -0.20).

[2] High risk of bias: unclear randomization (4/4), unclear allocation concealment (4/4), no or unclear blinding (2/4), unclear ITT analysis (1/4).

[3] Almost same group of trials as first analysis.

[4] High risk of bias: unclear randomization and allocation concealment in 14 studies.

[5] High risk of bias: unclear randomization and allocation concealment in 12 studies.

[6] CI includes -0.5.

[7] High risk of bias: unclear randomization (2/5), unclear allocation concealment (2/5), no or unclear blinding (2/5), no or unclear ITT analysis (2/5).

Referenties

1. Ameer F, Carson KV, Usmani ZA, Smith BJ. Ambulatory oxygen for people with chronic obstructive pulmonary disease who are not hypoxaemic at rest. Cochrane Database Syst Rev. 2014(6):CD000238.

2. Beaumont M, Forget P, Couturaud F, Reychler G. Effects of inspiratory muscle training in COPD patients: A systematic review and meta-analysis. Clin Respir J. 2018;12(7):2178-88.
3. Borge CR, Hagen KB, Mengshoel AM, Omenaas E, Moum T, Wahl AK. Effects of controlled breathing exercises and respiratory muscle training in people with chronic obstructive pulmonary disease: Results from evaluating the quality of evidence in systematic reviews. BMC polm. 2014;14(1).
4. Borge CR, Mengshoel AM, Omenaas E, Moum T, Ekman I, Lein MP, et al. Effects of guided deep breathing on breathlessness and the breathing pattern in chronic obstructive pulmonary disease: a double-blind randomized control study. Patient Educ Couns. 2015;98(2):182-90.
5. Ekström M, Ahmadi Z, Bornefalk-Hermansson A, Abernethy A, Currow D. Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy. Cochrane Database Syst Rev. 2016;11:CD006429.
6. Farquhar MC, Prevost AT, McCrone P, Brafman-Price B, Bentley A, Higginson IJ, et al. The clinical and cost effectiveness of a Breathlessness Intervention Service for patients with advanced non-malignant disease and their informal carers: mixed findings of a mixed method randomised controlled trial. Trials. 2016;17:185.
7. Gendron LM, Nyberg A, Saey D, Maltais F, Lacasse Y. Active mind-body movement therapies as an adjunct to or in comparison with pulmonary rehabilitation for people with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2018;10:CD012290.
8. Gu W-L, Liang Z-Y, Zhu C-B, Chen R-C. Clinical outcome of a novel breathing training maneuver in stable copd patients. International journal of clinical and experimental medicine [Internet]. 2018; 11(9):[9791 - pp.].
9. Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, Dzingina M, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. Lancet Respir Med. 2014;2(12):979-87.
10. Kaminsky DA, Guntupalli KK, Lippmann J, Burns SM, Brock MA, Skelly J, et al. Effect of Yoga Breathing (Pranayama) on Exercise Tolerance in Patients with Chronic Obstructive Pulmonary Disease: A Randomized, Controlled Trial. J Altern Complement Med. 2017;23(9):696-704.
11. Lee AL, Beauchamp MK, Goldstein RS, Brooks D. Clinical and physiological effects of rollators in individuals with chronic obstructive pulmonary disease: A systematic review. Journal of Cardiopulmonary Rehabilitation and Prevention. 2018;38(6):366-73.
12. Mayer AF, Karloh M, Dos Santos K, de Araujo CLP, Gulart AA. Effects of acute use of pursed-lips breathing during exercise in patients with COPD: a systematic review and meta-analysis. Physiotherapy. 2018;104(1):9-17.
13. Neves LF, Reis MH, Plentz RD, Matte DL, Coronel CC, Sbruzzi G. Expiratory and expiratory plus inspiratory muscle training improves respiratory muscle strength in subjects with COPD: systematic review. Respir Care. 2014;59(9):1381-8.
14. Ngai SP, Jones AY, Tam WW. Tai Chi for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2016(6):CD009953.
15. Qian Y, Wu Y, Rozman de Moraes A, Yi X, Geng Y, Dibaj S, et al. Fan Therapy for the Treatment of Dyspnea in Adults: A Systematic Review. Journal of Pain and Symptom Management. 2019;58(3):481-6.
16. Tan SB, Liam CK, Pang YK, Leh-Ching Ng D, Wong TS, Wei-Shen Khoo K, et al. The Effect of 20-Minute Mindful Breathing on the Rapid Reduction of Dyspnea at Rest in Patients With Lung Diseases: A Randomized Controlled Trial. Journal of Pain and Symptom Management. 2019;57(4):802-8.
17. Wu LL, Lin ZK, Weng HD, Qi QF, Lu J, Liu KX. Effectiveness of meditative movement on COPD: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2018;13:1239-50.

Onderzoeksvraag 6: Symptomen
Wat is het effect van medicatie op dyspneu bij mensen met COPD?

Patiënten	Patiënten met gevorderde COPD
Interventie	Medicamenteuze behandeling: 1. opioïden (morfine, fentanyl, oxycodon, hydromorfine), b. benzodiazepines, c. antidepressiva (sertraline, mirtazapine)
Comparator	Andere interventie, placebo, geen behandeling
Outcome	Kritisch: dyspneu, kwaliteit van leven, inspanningstolerantie Belangrijk: fysiek functioneren

Evidence tabellen
Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Ekström 2015	• Design: systematic review • Funding: Supported by the Swedish Society of Medicine, the Swedish Respiratory Society, the Swedish Heart-Lung Foundation, the Scientific Committee of Blekinge County Council, and the Wera and Emil Cornell Foundation; CoI: available online • Search date: Sep 2014 • Databases: CENTRAL, Medline, Embase, Cochrane metaanalysis, references, experts, textbooks • Study designs: RCTs • N included studies: N=16 including 271 patients	• Eligibility criteria: (1) randomized; (2) double blind; (3) any opioid as intervention; (4) placebo controlled; (5) outcomes included breathlessness, exercise capacity, or QOL; and (6) included at least one patient with COPD • Exclusion criteria were lack of an intention-to-treat analysis and any systematic difference in given treatment between the study groups other than the intervention studied	Opioids	CRITICAL OUTCOMES • Dyspnoea: opioids reduced breathlessness (12 studies, N=200; SMD -0.35; 95%CI -0.55 to -0.17). There was significant heterogeneity between studies of nebulized opioids (I^2 78.9%; p=0.003) but not between studies of systemic opioids (I^2 0%; p=0.438) ○ Systemic (8 studies, N=118): SMD -0.34 (95%CI -0.58 to -0.10; I^2 0%) ○ Nebulized (4 studies, N=82): SMD -0.39 (95%CI -0.71 to -0.07; I^2 78.9%) • Quality of life: no meta-analysis possible; reported in 3 studies: ○ Poole 1998: measured with Chronic Respiratory Questionnaire score; decreased slightly from baseline, -0.86 (pooled SD 15.1), after 6 weeks' opioid treatment compared with placebo ○ Abernethy 2003: no significant difference in overall wellbeing (categorical scale: poor, fair, good, or very good) after 4 days of morphine as compared with placebo (p=0.452)	Level of evidence: high risk of bias • No language restriction • Review process in duplicate, although not completely clear for risk of bias assessment

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				○ Shohrati 2012: global quality of life on a 100-mm visual analogue scale (VAS) increased after 5 days' opioid treatment by a mean 4.0 mm (pooled SD 6.2) over baseline compared with placebo • Exercise tolerance: no clear effect of opioids on exercise capacity (13 studies, N=149; SMD 0.06; 95%CI -0.15 to 0.28; I^2 70.7%) ○ Systemic (8 studies, N=92): SMD 0.11 (95%CI -0.17 to 0.39; I^2 63.3%) ○ Nebulized (6 studies, N=69): SMD -0.01 (95%CI -0.36 to 0.34; I^2 78.5%) IMPORTANT OUTCOMES • Physical functioning: not reported	
Simon 2016	• Design: systematic review • Funding: The Werner Jackstaedt Foundation, Germany; The Federal Ministry of Education and Research (BMBF; 01KG1509), Germany; CoI: one reviewer received reimbursement of travel costs from Teva Pharmaceutical Industries Ltd. • Search date: Aug 2016 • Databases: CENTRAL, CDSR, Medline, Embase, Cinahl, PsycINFO, ACP Journal Club, NHSEED, Halley Stewart Library, International	• Eligibility criteria: randomised controlled trials (RCTs) and controlled clinical trials (CCTs) assessing the effect of benzodiazepines compared with placebo or active control in relieving breathlessness in people with advanced stages of cancer, chronic obstructive pulmonary disease (COPD), chronic heart failure, motor neurone disease, and idiopathic pulmonary fibrosis	Benzodiazepines	CRITICAL OUTCOMES • Dyspnoea: no statistically significant effect of alprazolam, diazepam, or temazepam (4 studies, N=61; SMD -0.12; 95%CI -0.52 to 0.29; I^2 18%) • Quality of life: not reported • Exercise tolerance: ○ Eimer 1985: no difference between benzodiazepines and placebo on 12MWD ○ Woodcock 1981: significant impairment in 12MWD in the intervention group compared to placebo, and a non-significant decline in time to exhaustion on treadmill and workload on bicycle ergometer IMPORTANT OUTCOMES • Physical functioning: not reported	Level of evidence: high risk of bias • Review process in duplicate • No language restriction

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Pharmaceutical Abstracts, IDIS • Study designs: RCTs and CCTs • N included studies: N=8 (5 with COPD patients)				

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Abdallah 2017	• Design: cross-over RCT • Funding: available online; CoI: available online • Setting: single-centre study, McGill University, Canada • Sample size: N=23 • Duration: unclear	• Eligibility criteria: patients ≥40y, GOLD 3-4 COPD, chronic breathlessness syndrome [5], defined as a modified MRC dyspnoea score of ≥3, a baseline dyspnoea index focal score of ≤6 and/or an oxygen cost diagram rating of ≤50% full scale despite optimal treatment with bronchodilators, corticosteroids and/or phosphodiesterase inhibitors • *A priori* patient characteristics: ○ Mean age: 63.6 ○ Men: 75% ○ GOLD 4: 40% ○ Mean FEV_1: 0.93	Morphine (oral, immediate-release, 0.1 mg/kg body mass to a maximum dose of 10 mg) vs. Placebo	CRITICAL OUTCOMES • Dyspnoea: Compared with placebo ○ Morphine decreased breathlessness intensity ratings at isotime by 1.2 +/- 0.4 Borg-units (p=0.011) ○ Morphine decreased breathlessness unpleasantness ratings by 1.4 +/- 0.4 Borg-units at isotime (p=0.003) • Quality of life: not reported • Exercise tolerance: compared with placebo, morphine increased EET by 2.5 +/- 0.9 min (148 +/- 52 s) or 41±13% (p=0.014) IMPORTANT OUTCOMES • Physical functioning: not reported	Level of evidence: high risk of bias • Unclear randomisation and allocation concealment • 3 patients excluded from analysis (no cross-over for several reasons, 1 because of serious adverse event) • Double-blinded
Janowiak 2017	• Design: cross-over RCT • Funding: financed by the Medical University of Gdansk internal grant no. ST-553; CoI: one author is the manufacturer of the	• Eligibility criteria: (a) age above 50 years; (b) diagnosis of COPD group D, according to GOLD guidelines; (c) stage IV airflow limitation i.e. FEV_1% < 30%; (d) breathlessness rated 3 or 4 in the	Morphine (nebulized), 2% morphine hydrochloride water solution, once daily during four-day period	CRITICAL OUTCOMES • Dyspnoea: All patients experienced clinically and statistically significant (p < 0.0001) breathlessness reduction during morphine nebulization:	Level of evidence: high risk of bias • Simple randomisation • Allocation concealment • Double blinded

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	inhalation device used in the study (PNEUMONEB®) • Setting: single-centre, University Clinical Centre, Gdańsk, Poland • Sample size: N=11 • Duration:	mMRC breathlessness scale; (e) current non-smoker; (f) written informed consent • Exclusion criteria included: (a) other coexisting severe chronic lung diseases, such as lung cancer; (b) breathlessness caused by other than COPD chronic diseases, such as heart failure or renal failure; (c) inability to give informed consent; (d) previous history of respiratory depression after opioid administration or allergic reactions to opioids; (e) ongoing opioid treatment for any indication; and (f) COPD exacerbation within the last month • *A priori* patient characteristics: ○ Mean age: 67.2y ○ Men: 80% ○ Mean FEV_1: 27.5%	vs. NaCl	○ Mean VAS changes for morphine and 0.9% NaCl periods were 25.4 mm (SD 9.0) and 6.3 mm (SD 7.8), respectively • Quality of life: not reported • Exercise tolerance: significant improvement ($p<0.05$) in Wilcock's test, independent of the substance used, in both groups; no significant difference IMPORTANT OUTCOMES • Physical functioning: not reported	• Due to the observed, bigger than expected, differences in VAS scores between the two study arms, the trial needed to be stopped, ethically, after 10 of 11 admitted patients completed study protocol

Abbreviations: 95%CI: 95% confidence interval; BMI: body mass index; CoI: conflicts of interest; COPD: chronic obstructive pulmonary disease; EET: exercise endurance time; FEV_1: forced expiratory volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; MD: mean difference; MRC: Medical Research Council; QOL: quality of life; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference; VAS: visual analogue scale.

GRADE profielen

Opioids: general

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opioids	Control	Relative (95%CI)	Absolute		
Dyspnoea												

12	RCT	Serious[1]	Serious[2]	No serious indirectness	Serious[3]	None	?	?	SMD -0.35 -0.55 to -0.17	-	VERY LOW	CRITICAL
1	RCT	Serious[4]	No serious inconsistency	No serious indirectness	No serious imprecision[5]	None	10	10	-	Mean VAS changes for morphine and 0.9% NaCl periods were 25.4 mm (SD 9.0) and 6.3 mm (SD 7.8), respectively	MODERATE	CRITICAL
1	RCT	Serious[6]	No serious inconsistency	No serious indirectness	Serious[7]	None	20	20	-	Morphine decreased breathlessness intensity ratings at isotime by 1.2 +/- 0.4 Borg-units (p=0.011) Morphine decreased breathlessness unpleasantness ratings by 1.4 +/- 0.4 Borg-units at isotime (p=0.003)	LOW	CRITICAL
Quality of life												
3	RCT	Serious[1]	Serious[8]	No serious indirectness	Serious[9]	None	?	?	-	See evidence tables	VERY LOW	CRITICAL
Exercise tolerance												
13	RCT	Serious[1]	Serious[10]	No serious indirectness	No serious imprecision	None	?	?	SMD 0.06 -0.15 to 0.28	-	LOW	CRITICAL
1	RCT	Serious[4]	No serious inconsistency	No serious indirectness	Serious[9]	None	10	10	-	Significant improvement	LOW	CRITICAL

										(p<0.05) in Wilcock's test, independent of the substance used, in both groups; no significant difference		
1	RCT	Serious[6]	No serious inconsistency	No serious indirectness	Serious[11]	None	20	20	-	Compared with placebo, morphine increased EET by 2.5 +/- 0.9 min (148 +/- 52 s) or 41±13% (p=0.014)	LOW	CRITICAL
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: possible issues with randomization, allocation concealment, blinding and/or ITT analysis in most studies.

[2] Visual inconsistency on forest plot.

[3] CI includes -0.5.

[4] Prematurely stopped.

[5] SMD 2.17, 95%CI 1.02 to 3.33.

[6] Unclear randomisation and allocation concealment; 3 drop-outs.

[7] CI around SMD includes -0.5.

[8] Discordant results across three studies.

[9] Not possible to evaluate.

[10] I^2 70.7%.

[11] CI around SMD includes 0.5.

Opioids: systemic

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Opioids**	**Control**	**Relative (95%CI)**	**Absolute**		

Dyspnoea												
8	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	?	?	SMD -0.34 -0.58 to -0.10	-	LOW	CRITICAL
1	RCT	Serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	20	20	-	Morphine decreased breathlessness intensity ratings at isotime by 1.2 +/- 0.4 Borg-units (p=0.011) Morphine decreased breathlessness unpleasantness ratings by 1.4 +/- 0.4 Borg-units at isotime (p=0.003)	LOW	CRITICAL
Quality of life												
2	RCT	Serious[5]	Serious[6]	No serious indirectness	Serious[7]	None	?	?	-	See evidence tables	VERY LOW	CRITICAL
Exercise tolerance												
8	RCT	Serious[1]	Serious[8]	No serious indirectness	No serious imprecision	None	?	?	SMD 0.11 -0.17 to 0.39	-	LOW	CRITICAL
1	RCT	Serious[3]	No serious inconsistency	No serious indirectness	Serious[9]	None	20	20	-	Compared with placebo, morphine increased EET by 2.5 +/- 0.9 min (148 +/- 52 s) or 41±13% (p=0.014)	LOW	CRITICAL
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: possible issues with randomization, allocation concealment, blinding and/or ITT analysis in most studies.
[2] CI includes -0.5.
[3] Unclear randomisation and allocation concealment; 3 drop-outs.
[4] CI around SMD includes -0.5.
[5] One study with low risk of bias, one study with unclear risk of bias.
[6] Discordant results.
[7] Not possible to evaluate.
[8] I^2 63.3%.
[9] CI around SMD includes 0.5.

Opioids: nebulized

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Opioids**	**Control**	**Relative (95%CI)**	**Absolute**		
Dyspnoea												
4	RCT	Serious[1]	Serious[2]	No serious indirectness	Serious[3]	None	?	?	SMD -0.39 -0.71 to -0.07	-	VERY LOW	CRITICAL
1	RCT	Serious[4]	No serious inconsistency	No serious indirectness	No serious imprecision[5]	None	10	10	-	Mean VAS changes for morphine and 0.9% NaCl periods were 25.4 mm (SD 9.0) and 6.3 mm (SD 7.8), respectively		
Quality of life												
1	RCT	Serious[6]	No serious inconsistency	No serious indirectness	Serious[7]	None	?	?	-	See evidence tables	LOW	CRITICAL
Exercise tolerance												
6	RCT	Serious[1]	Serious[8]	No serious indirectness	No serious imprecision	None	?	?	SMD -0.01 -0.36 to 0.34	-	LOW	CRITICAL

1	RCT	Serious[4]	No serious inconsistency	No serious indirectness	Serious[7]	None	10	10	-	Significant improvement (p<0.05) in Wilcock's test, independent of the substance used, in both groups; no significant difference	LOW	CRITICAL
Physical functioning												
0	No evidence											IMPORTANT

[1] High risk of bias: possible issues with randomization, allocation concealment, blinding and/or ITT analysis in most studies.

[2] I^2 78.9%.

[3] CI includes -0.5.

[4] Prematurely stopped.

[5] SMD 2.17, 95%CI 1.02 to 3.33.

[6] Unclear risk of bias.

[7] Not possible to evaluate.

[8] I^2 78.5%.

Benzodiazepines

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Benzodiazepines**	**Control**	**Relative (95%CI)**	**Absolute**		
Dyspnoea												
4	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	61	61	SMD -0.12 (-0.52 to 0.29)	-	LOW	CRITICAL
Quality of life												
0	No evidence											CRITICAL

Exercise tolerance											
2	RCT	Serious[3]	Serious[4]	No serious indirectness	Serious[5]	None	20	20	-	See evidence tables	VERY LOW	CRITICAL
Physical functioning											
0	No evidence										IMPORTANT

[1] High risk of bias: possible issues with randomization and allocation concealment in all studies, unclear ITT analysis in three studies.

[2] CI includes -0.5.

[3] High risk of bias: possible issues with randomization and allocation concealment in both studies, unclear blinding in one study.

[4] Inconsistent results.

[5] Not possible to evaluate.

Referenties

1. Abdallah SJ, Wilkinson-Maitland C, Saad N, Li PZ, Smith BM, Bourbeau J, et al. Effect of morphine on breathlessness and exercise endurance in advanced COPD: a randomised crossover trial. The European respiratory journal. 2017;50(4).
2. Abernethy AP, Currow DC, Frith P, Fazekas BS, McHugh A, Bui C. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. Bmj. 2003;327(7414):523-8.
3. Eimer M, Cable T, Gal P, Rothenberger LA, McCue JD. Effects of clorazepate on breathlessness and exercise tolerance in patients with chronic airflow obstruction. J Fam Pract. 1985;21(5):359-62.
4. Ekström M, Nilsson F, Abernethy AA, Currow DC. Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review. Ann Am Thorac Soc. 2015;12(7):1079-92.
5. Janowiak P, Krajnik M, Podolec Z, Bandurski T, Damps-Konstanska I, Sobanski P, et al. Dosimetrically administered nebulized morphine for breathlessness in very severe chronic obstructive pulmonary disease: a randomized, controlled trial. BMC polm. 2017;17(1):186.
6. Poole PJ, Veale AG, Black PN. The effect of sustained-release morphine on breathlessness and quality of life in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;157(6 Pt 1):1877-80.
7. Simon S, Higginson I, Booth S, Harding R, Weingärtner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database Syst Rev [Internet]. 2016; (10).
8. Shohrati M, Ghanei M, Harandi AA, Foroghi S, Harandi AA. Effect of nebulized morphine on dyspnea of mustard gas-exposed patients: a double-blind randomized clinical trial study. Pulm Med. 2012;2012:610921.
9. Woodcock AA, Gross ER, Geddes DM. Oxygen relieves breathlessness in "pink puffers". Lancet. 1981;1(8226):907-9.

Onderzoeksvraag 7: Symptomen
Wat is het effect van behandeling op prikkelhoest bij patiënten met gevorderde COPD?

Patiënten Patiënten met COPD in de palliatieve fase
Interventie Opioïden, hoestdempende middelen, fysiotherapeutische interventies (hoesttechnieken en ademhalingsoefeningen)
Comparator Geen behandeling, placebo, andere interventie
Outcome Kritisch: hoesten, vrijmaken luchtwegen

Evidence tabellen
Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Molassiotis 2010	• Design: systematic review • Funding: not reported; CoI: authors report having no CoI • Search date: April 2009 • Databases: MEDLINE, EMBASE, CINAHL, British Nursing Index, PsychINFO, Science Citation Index Expanded, etc • Study designs: RCTs, trials with comparative arm • N included studies: N=75 (18 with COPD, but only 2 with relevant intervention)	• Eligibility criteria: adult patients with respiratory and non-respiratory diseases (excluding cancer) that had acute or chronic cough • Exclusion: upper respiratory tract infection; cough sensitive, animal and paediatric studies	Pharmacological and non-pharmacological interventions	CRITICAL OUTCOMES • Cough: o Codeine: ▪ Smith 2006: see below o Lidocaine: ▪ Chong 2005: see below • Airway clearance: not reported	Level of evidence: high risk of bias • Limited to English language • Review process in duplicate • Jadad-scale used for quality appraisal

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Chong 2005	• Design: RCT • Funding: not reported; CoI: none declared • Setting: Shin-Kong Wu Ho-Su Memorial Hospital, Taipei City, Taiwan • Sample size: N=127 • Duration: 6-month period in 2003	• Eligibility criteria: COPD patients with intractable coughing; excluded: dyspnoea, unstable vital signs, and pneumonia or neoplasm on chest X-ray • *A priori* patient characteristics: ○ Mean age: 69.2 (SD 12.1) ○ Female: 33.1 %	Lidocaine (N=62) vs. Bronchodilator inhalation treatment (N=65)	CRITICAL OUTCOMES • Cough: ○ Media cough severity score one hour post-treatment: lidocaine from 8 to 3 (p<0.01); bronchodilator from 8 to 3 (p<0.01); no difference between both groups (p=0.44) • Airway clearance: not reported	Level of evidence: high risk of bias • Unclear randomisation method • Opaque sealed envelopes, but unclear who allocated groups • Blinding of patients and clinicians, but not of the nurses who delivered treatment • Intention-to-treat analysis
Smith 2006	• Design: cross-over RCT • Funding: educational grant by GlaxoSmithKline; CoI: authors declared to have no CoI • Setting: University hospitals at Manchester and Liverpool, UK • Sample size: N=21 • Duration: 7-10 days	• Eligibility criteria: patients with stable COPD (FEV_1 30-75% predicted), complaining of coughing, and with more than 80 coughing seconds (cs) on 20 hours monitoring; • Exclusion: patients with exacerbations in last month, previous acute hypercapnic ventilator failure, low oxygen saturation, current smokers or asthma • *A priori* patient characteristics: ○ Mean age: 68 years ○ Male: 76.9% ○ Mean predictive FEV_1: 53.4% ○ Median smoking history: 43.5 pack-years	Codeine phosphate (60 mg) vs. Placebo	CRITICAL OUTCOMES • Cough: ○ Median cough rate in coughing seconds: baseline 8.27 cs/h (IQR 5.94-11.67); placebo 7.22 (4.42-10.40); codeine 6.41 (3.86-9.10) ▪ Codeine vs baseline (p=0.02) ▪ Codeine vs placebo (p=0.52) ○ Citric acid cough threshold: no significant difference among codeine, placebo, and baseline for cough reflex sensitivity as measured by log C5 or log C2 (Friedman test, p=0.12 and p=0.46, respectively) ○ Cough score (mean, SD): ▪ Day: baseline 2.8 (0.7), placebo 2.7 (0.6), codeine 2.8 (1.0); p=0.59 ▪ Night: baseline 1.7 (1.0), placebo 1.7 (1.2), codeine 1.4 (0.9); p=0.50 ○ Cough VAS (median, IQR): ▪ Day: baseline 44 (32-66), placebo 27 (11-61), codeine 24 (11-63); p=0.11 ▪ Night: baseline 12 (8-38), placebo 17 (12-47), codeine 7 (6-19); p=0.25 • Airway clearance: not reported	Level of evidence: moderate risk of bias • Unclear randomisation method • Allocation was concealed by the use of numbered containers for study medication; done independently by hospital pharmacy • Blinded (identical appearance of capsules) • Blinded analysis of data • 2 drop-outs

Abbreviations: CoI: conflict of interest; COPD: chronic obstructive pulmonary disease; CPT: chest physical therapy; cs: coughing seconds; FEV_1: forced expiratory volume in 1 second; IQR: interquartile range; PEP: positive expiratory pressure; RCT: randomised controlled trial; SD: standard deviation.

GRADE profielen

Lidocaine vs. bronchodilator inhalation treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lidocaine**	**Control**	**Relative (95%CI)**	**Absolute**		
Median cough severity 1h post-treatment												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	62	65	-	3 vs. 3 p=0.44	LOW	CRITICAL

[1] High risk of bias: possible issues with randomization and allocation concealment, no blinding of nurses who delivered treatment.

[2] No relative effect reported, no information on 95%CI.

Codeine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Codeine**	**Control**	**Relative (95%CI) $**	**Absolute**		
Median cough rate (coughing seconds)												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	19	19	Estimated SMD = -0.19 (-0.83 to 0.44)	6.41 vs. 7.22 cs/h p=0.52	LOW	CRITICAL
Citric acid cough threshold												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	19	19	-	No significant difference among codeine, placebo, and baseline for cough reflex sensitivity as	LOW	CRITICAL

										measured by log C5 or log C2 (Friedman test, p=0.12 and p=0.46, respectively)		
Cough score: mean (SD)												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Day very serious, night serious[4]	None	19	19	Day: SMD = 0.12 (-0.52 to 0.76) Night: SMD = -0.31 (-0.95 to 0.33)	Day: baseline 2.8 (0.7), placebo 2.7 (0.6), codeine 2.8 (1.0); p=0.59 Night: baseline 1.7 (1.0), placebo 1.7 (1.2), codeine 1.4 (0.9); p=0.50	Day: VERY LOW Night: LOW	CRITICAL
Cough VAS: median (IQR)												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Day very serious, night serious[4]	None	19	19	Day: Estimated SMD = -0.01 (-0.64 to 0.63) Night: Estimated SMD = -0.68 (-1.34 to -0.02)	Day: baseline 44 (32-66), placebo 27 (11-61), codeine 24 (11-63); p=0.11 Night: baseline 12 (8-38), placebo 17	Day: VERY LOW Night: LOW	CRITICAL

										(12-47), codeine 7 (6-19); p=0.25		

[$] If median and IQR reported, mean and SD were calculated using the method of Wan et al.: Wan, X., Wang, W., Liu, J. *et al.* Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* **14,** 135 (2014). https://doi.org/10.1186/1471-2288-14-135. Mean and SD were then used to calculate the SMD and 95%CI.

[1] Moderate risk of bias: unclear randomization method.

[2] 95%CI includes -0.5.

[3] Relative effect not reported.

[4] Day: 95%CI includes -0.5 and 0.5; night: 95%CI includes -0.5.

Referenties

1. Bellone A, Spagnolatti L, Massobrio M, Bellei E, Vinciguerra R, Barbieri A, et al. Short-term effects of expiration under positive pressure in patients with acute exacerbation of chronic obstructive pulmonary disease and mild acidosis requiring non-invasive positive pressure ventilation. Intensive Care Med. 2002;28(5):581-5.
2. Chong CF, Chen CC, Ma HP, Wu YC, Chen YC, Wang TL. Comparison of lidocaine and bronchodilator inhalation treatments for cough suppression in patients with chronic obstructive pulmonary disease. Emerg Med J. 2005;22(6):429-32.
3. Kodric M, Garuti G, Colomban M, Russi B, Porta RD, Lusuardi M, et al. The effectiveness of a bronchial drainage technique (ELTGOL) in COPD exacerbations. Respirology. 2009;14(3):424-8.
4. May DB, Munt PW. Physiologic effects of chest percussion and postural drainage in patients with stable chronic bronchitis. Chest. 1979;75(1):29-32.
5. Molassiotis A, Bryan G, Caress A, Bailey C, Smith J. Pharmacological and non-pharmacological interventions for cough in adults with respiratory and non-respiratory diseases: A systematic review of the literature. Respir Med. 2010;104(7):934-44.
6. Oldenburg FA, Jr., Dolovich MB, Montgomery JM, Newhouse MT. Effects of postural drainage, exercise, and cough on mucus clearance in chronic bronchitis. Am Rev Respir Dis. 1979;120(4):739-45.
7. Olseni L, Midgren B, Hornblad Y, Wollmer P. Chest physiotherapy in chronic obstructive pulmonary disease: forced expiratory technique combined with either postural drainage or positive expiratory pressure breathing. Respir Med. 1994;88(6):435-40.
8. Smith J, Owen E, Earis J, Woodcock A. Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2006;117(4):831-5.