

Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis

Supplement: content

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TABLE S1a. Search strategy in Pubmed	
Breathlessness	<ol style="list-style-type: none"> 1. dyspnoea/drug therapy[Mesh Terms] 2. dyspn*[Title/Abstract] 3. breathless*[Title/Abstract] 4. ((breath*[Title/Abstract]) AND labour*[Title/Abstract]) 5. ((short*[Title/Abstract]) AND breath*[Title/Abstract]) 6. breathing difficult*[Title/Abstract] 7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
Opioid	<ol style="list-style-type: none"> 8. analgesics, opioid/adverse effects[Mesh Terms] 9. analgesics, opioid/therapeutic use[Mesh Terms] 10. opioid*[Title/Abstract] 11. opiate*[Title/Abstract] 12. codeine/adverse effects[Mesh Terms] 13. codeine/therapeutic use[Mesh Terms] 14. codeine[Title/Abstract] 15. heroin/adverse effects[Mesh Terms] 16. heroin/therapeutic use[Mesh Terms] 17. diamorphine[Title/Abstract] 18. fentanyl/adverse effects[Mesh Terms] 19. fentanyl/therapeutic use[Mesh Terms] 20. fentanyl[Title/Abstract] 21. dihydrocodeine[Supplementary Concept] 22. dihydrocodeine[Title/Abstract] 23. morphine/adverse effects[Mesh Terms] 24. morphine/therapeutic use[Mesh Terms] 25. morphine[Title/Abstract] 26. oxycodone/adverse effects[Mesh Terms] 27. oxycodone/therapeutic use[Mesh Terms] 28. oxycodone[Title/Abstract] 29. 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28
	30. animals[Mesh Terms] NOT humans[Mesh Terms]
	31. (#7 AND #29) NOT #30
	32. Limit #31 to article types case reports, clinical studies, clinical trials, comparative studies, multicentre studies, observational studies, randomized controlled trials.

TABLE S1b. Search strategy in Embase	
Breathlessness	<ol style="list-style-type: none"> 1. exp dyspnea/dt [Drug Therapy] 2. dyspn*.mp [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 3. breathless*.mp 4. "breath* labour*".mp 5. "short* of breath*".mp 6. "breath* difficult*".mp 7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
Opioids	<ol style="list-style-type: none"> 8. exp opiate/ae, dt [Adverse Drug Reaction, Drug Therapy] 9. opioid*.mp 10. opiate*.mp 11. exp codeine/ae, dt [Adverse Drug Reaction, Drug Therapy] 12. codeine.mp 13. exp diamorphine/ae, dt [Adverse Drug Reaction, Drug Therapy] 14. diamorphine.mp 15. exp fentanyl/ae, dt [Adverse Drug Reaction, Drug Therapy] 16. fentanyl.mp 17. exp dihydrocodeine/ae, dt [Adverse Drug Reaction, Drug Therapy] 18. dihydrocodeine.mp

	19. exp morphine/ae, dt [Adverse Drug Reaction, Drug Therapy]
	20. morphine.mp
	21. exp oxycodone/ae, dt [Adverse Drug Reaction, Drug Therapy]
	22. oxycodone.mp
	23. 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22
	24. 7 AND 23
	25. Limit 24 to human
	26. Limit 25 publication type to <i>Journal: Article</i>

TABLE S1c. Search strategy in CENTRAL

Breathlessness	1. MeSH descriptor: [Dyspnea] explode all trees and with qualifier(s): [Drug therapy – DT] 2. dyspn*.ti,ab,kw (Word variations have been searched) 3. breathless*.ti,ab,kw (Word variations have been searched) 4. “breath* labour*”.ti,ab,kw (Word variations have been searched) 5. “short* of breath*”.ti,ab,kw (Word variations have been searched) 6. “breath* difficult*”.ti,ab,kw (Word variations have been searched) 7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
Opioids	8. MeSH descriptor: [Analgesics, Opioid] explode all trees and with qualifier(s): [Adverse effects – AE, Therapeutic use – TU] 9. opioid*.ti,ab,kw (Word variations have been searched) 10. opiate*.ti,ab,kw (Word variations have been searched) 11. MeSH descriptor: [Codeine] explode all trees and with qualifier(s): [Adverse effects – AE, Therapeutic use – TU] 12. codeine.ti,ab,kw (Word variations have been searched) 13. MeSH descriptor: [Heroin] explode all trees and with qualifier(s): [Adverse effects – AE, Therapeutic use – TU] 14. diamorphine.ti,ab,kw (Word variations have been searched) 15. MeSH descriptor: [Fentanyl] explode all trees and with qualifier(s): [Adverse effects – AE, Therapeutic use – TU] 16. fentanyl.ti,ab,kw (Word variations have been searched) 17. dihydrocodeine.ti,ab,kw (Word variations have been searched) 18. MeSH descriptor: [Morphine] explode all trees and with qualifier(s): [Adverse effects – AE, Therapeutic use – TU] 19. morphine.ti,ab,kw (Word variations have been searched) 20. MeSH descriptor: [Oxycodone] explode all trees and with qualifier(s): [Adverse effects – AE, Therapeutic use – TU] 21. oxycodone.ti,ab,kw (Word variations have been searched) 22. #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
	23. #7 AND #22
	24. Limit #23 to <i>trials</i>

TABLE S1d. Search strategy in CINAHL

Breathlessness	1. (MH “Dyspnea+/DT”) 2. TI dyspn* OR AB dyspn* 3. TI breathless* OR AB breathless* 4. TI “breath* labour*” OR AB “breath* labour*” 5. TI “short* of breath*” OR AB “short* of breath*” 6. TI “breath* difficult*” OR AB “breath* difficult*” 7. S1 OR S2 OR S3 OR S4 OR S5 OR S6
Opioids	8. (MH “Analgesics, Opioid+/AE/TU”) 9. TI opioid* OR AB opioid* 10. TI opiate* OR AB opiate* 11. (MH “Codeine+/AE/TU”) 12. TI codeine OR AB codeine

	13. (MH "Heroin+/AE/TU ") 14. TI diamorphine OR AB diamorphine 15. (MH "Fentanyl+/AE/TU ") 16. TI fentanyl OR AB fentanyl 17. TI dihydrocodeine OR AB dihydrocodeine 18. (MH "Morphine+/AE/TU ") 19. TI morphine OR AB morphine 20. (MH "Oxycodone+/AE/TU ") 21. TI oxycodone OR AB oxycodone 22. S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21
	23. S7 AND S21; Limiters - Human

TABLE S1e. Search strategy in ClinicalTrials.gov

Breathlessness	1. Dyspnea (condition/disease) 2. Dyspnea (other terms) 3. Dyspnoea (other terms) 4. Breathlessness (condition/disease) 5. Breathlessness (other terms) 6. Breath shortness (condition/disease) 7. S1 OR S2 OR S3 OR S4 OR S5 OR S6
Opioids	8. Opioids (intervention/treatment) 9. Opioid analgesic (intervention/treatment) 10. Analgesics, opioid (intervention/treatment) 11. Opiate (intervention/treatment) 12. Opioid (other terms) 13. Analgesic (other terms) 14. Codeine (intervention/treatment) 15. Codeine (other terms) 16. Diamorphine (intervention/treatment) 17. Diamorphine (other terms) 18. Fentanyl (intervention/treatment) 19. Fentanyl (other terms) 20. Dihydrocodeine (intervention/treatment) 21. Dihydrocodeine (other terms) 22. Morphine (intervention/treatment) 23. Morphine (other terms) 24. Oxycodone (intervention/treatment) 25. Oxycodone (other terms) 26. S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25
	27. S7 AND S26

TABLE S2. Patient characteristics, study design and results of observational studies										
Study	Design	N (% men)	Population (n)	Age (yr)	Opioid	Dose (mg/day)	Administration	Duration	Patient setting	Outcomes: difference <i>Definition of RD</i>
Allen, 2005 [1]	Pro- spective	11 (27)	IPF (11)	Mean 68 (range 78-92)	Diamorphine	2.5-5.0 mg	Parenteral	Single dose	Inpatient	SaO ₂ : 0% RR: -2 breaths/minute RD: 0 <i>Change in vital signs or oxygen saturation</i>
Colman, 2015 [2]	Retro- spective	64 (45) 59 received opioids	Patients awaiting lung transplantation; ILD (51) BO (5) COPD (4) PH (4)	Mean 59.4 (SD 9.4)	Morphine or hydromorphone ¹	Median dose: SR: 30 MED (range 20-840) IR: 15 MED (range 6-60) AN: no data	Oral	Median follow-up: 153 days	Inpatient/ outpatient	RD: 0
Farncombe, 1994 [3]	Retro- spective	54 (43)	Cancer (40) ORD (3) RRD (3) cardiac disease (6) AIDS (1) bowel obstruction (1)	Median 62 (range 21-90)	Morphine ² Hydromorphone ² Codeine ² Anileridine ²	30-180 6-120 90-360 150-300	Nebulized	1-3 doses (12) 1-2 days (8) 3-14 days (17) > 15 days (17)	Inpatient/ outpatient	PaCO ₂ : no significant change (n=4) SaO ₂ : no significant change (n=4) RR: 10-30% decrease, but non below 16 breaths/minute (n=8)
Hu, 2014 [4]	Pro- spective	136 (57) 27 used opioid for breathlessness at admission and 36 2 days prior to death	Cancer (136)	≤ 18 (3) 19-35 (6) 36-50 (27) 51-64 (31) ≥ 65 (69)	Morphine	At admission: Mean 37.7 MED (SD 38.6) Prior to death: Mean 44.7 MED (SD 52.3)	Oral, parenteral, or combined	No data	Inpatient	RD: 1 (also at start of study) <i>Decrease in RR to less than 10 times per minute.</i>
Kanemoto, 2007 [5]	Retro- spective	337 (74) 92 reported breathlessness and received morphine	Cancer (212) IIP/CDPF (47) Pneumonia (41) COPD (22) Bronchiectasis (7) Tuberculosis (3) Pyothorax (2) PH (1) Thromboembolism (1) Pneumoconiosis (1)	Median 72 (range 22-96)	Morphine	No data	Parenteral	No data	Inpatient	RD: 0
Kawabata, 2013 [6]	Retro- spective	95 (55) 44 administrations for episodes of	Cancer (95)	Mean 71.7 (range 47-92)	Oxycodone ²	Mean 44.6 (range 5.5-206.6)	Parenteral	Mean: 14.4 days	Inpatient	RD: 3

TABLE S2. Patient characteristics, study design and results of observational studies										
Study	Design	N (% men)	Population (n)	Age (yr)	Opioid	Dose (mg/day)	Administration	Duration	Patient setting	Outcomes: difference Definition of RD
		breathlessness								
Oxberry, 2013 [7]	Pro- spective	33 (85)	CHF (33)	Mean 71.9 (SD 9.1)	Morphine or oxycodone vs. placebo	Morphine: 20 Oxycodone: 10	Oral	3 months	Outpatient	SaO ₂ : -1% in users, +1% in non-users RR: -1 breaths/minute in users, -2 breaths/ minute in non-users
Pang, 2016 [8]	Pro- spective	16 (50)	Cancer (16)	Mean 63.6 SD (13.5)	Fentanyl	Responders: 0.22 (0.17) Non-responders: 0.28 (0.20)	Parenteral	24 hours	Inpatient	RR: -4 breaths/minute in responders; -2 breaths/minute in non-responders ³
Sporer, 2006 [9]	Retro- spective	319 (47) 20 received morphine	ADHF (319)	Mean 77 (SD 12)	Morphine	No data	No data	No data	Outpatient	SaO ₂ : no change (no data shown) RR: no change (no data shown)

ADHF: acute decompensated heart failure; AIDS: acquired immune deficiency syndrome; AN: opioids on “as needed” basis; BO: bronchiolitis obliterans; CDPF: collagen disease-related pulmonary fibrosis; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; IIP: idiopathic interstitial pneumonia; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; IR: immediate-release opioids; MED: morphine equivalent dose; ORD: obstructive respiratory disease; PaCO₂: partial pressure of arterial carbon dioxide; PaO₂: partial pressure of arterial oxygen; PH: pulmonary hypertension; RD: respiratory depressions; RR: respiratory rate; RRD: restrictive respiratory disease; SaO₂: arterial oxygen saturation; SR: sustained-release opioids

¹ intervention is started on an as needed basis and transitioned to standing immediate-release opioids or sustained release opioids (with or without immediate-release opioids as needed) as tolerated;

² application of opioid for breakthrough breathlessness possible

³ median change

TABLE S3. Patient characteristics and results of case reports										
Study	Gender	Diagnosis	Age (yr)	Opioid	Dose	Administration	Duration	Pre-treatment?	Patient setting	Outcomes
Benitez-Rosario, 2005 [10]	Female	Lung cancer	67	Fentanyl ¹	1200 µg	Oral	Single dose	400 mg intravenous morphine/day	Inpatient	SaO ₂ : 90 to 91% RR: 22 to 14 breaths/minute
	Male	Lung cancer	52	Fentanyl ¹	400 µg	Oral	2 doses in 30 min	90 mg SR morphine/day	Inpatient	SaO ₂ : remained 93% RR: 20 to 18 breaths/minute
	Female	Colon cancer	57	Fentanyl ¹	400 µg	Oral	Single dose	15 mg intravenous morphine/day	Inpatient	SaO ₂ : remained 89% RR: remained 20 breaths/minute
Farncombe, 1993 [11]	Male	IPF	73	Morphine	30-150 mg	Nebulized	3 months	No	Inpatient	RR: slight decrease RD: no
	Male	IPF	68	Morphine	30-105 mg	Nebulized	At least 2 weeks	No	Inpatient	RD: no
	Male	CAD and COPD	74	Morphine	2.5 mg	Nebulized	Single dose	Intravenous morphine	Inpatient	PaCO ₂ : 7.2 to 6.4 kPa PaO ₂ : 8.5 to 9.9 kPa SaO ₂ : 87 to 93% RR: 32 to 28 breaths/minute RD: no
	Female	CHF and COPD	72	Morphine	2.5 mg	Nebulized	Single dose	Intravenous morphine	Inpatient	PaCO ₂ : 4.8 to 4.7 kPa PaO ₂ : 12.4 to 12.7 kPa SaO ₂ : remained 98% RR: 30 to 26 breaths/minute RD: no
Farncombe, 1994 [12]	Male	Lung cancer, CHF and COPD	91	Morphine	60-90 mg/day	Nebulized	At least 2 days	30 mg nebulized morphine/day	Inpatient	RR: 36 to 26 breaths/minute
	Female	Lung cancer	61	Hydro-morphone ¹	48 mg/day	Nebulized	No data	± 480 mg oral hydro-morphone/day	Outpatient	RR: 34 to 26 breaths/minute
Lang, 1997 [13]	Female	Probably primary lung cancer with metastases	74	Morphine ¹	4 mg	Nebulized	Single dose	30 mg oral morphine/day	Inpatient	RD: yes
Sitte, 2008 [14]	Male	Lung cancer	73	Fentanyl ¹	150 µg	Nasal	Single dose	No data	Outpatient	SaO ₂ : 62 to 94% RR: 30 to 12 breaths/minute RD: no
	Female	CHF, COPD and PH	88	Fentanyl ¹	1000 µg	Nasal	Single dose	No data	Outpatient	SaO ₂ : 65 to 75% RR: 40-50 to 20 breaths/minute RD: no
	Male	ILD	72	Fentanyl ¹	400 µg/administration	Nasal	Two weeks	No	Outpatient	RD: no
Sitte,	Male	COPD and lung	85	Fentanyl ¹	2000-4000	Nasal	No data	32 mg SR	Outpatient	RD: no

TABLE S3. Patient characteristics and results of case reports										
Study	Gender	Diagnosis	Age (yr)	Opioid	Dose	Administration	Duration	Pre-treatment?	Patient setting	Outcomes
2009 [15]		cancer			µg/day			hydromorphone/day		
	Male	Lung cancer	53	Fentanyl	1200 µg/day + 200 µg/episode	Parenteral and nasal	No data	No data	Outpatient	RD: no

CAD: coronary artery disease; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; PaCO₂: partial pressure of arterial carbon dioxide; PaO₂: partial pressure of arterial oxygen; PH: pulmonary hypertension; RD: respiratory depressions; RR: respiratory rate; SaO₂: arterial oxygen saturation; SR: sustained-release.

¹ intervention prescribed for an episode of breakthrough breathlessness

TABLE S4. Characteristics and study design of ongoing studies											
Study name	Clinical-Trials number	Design	Estimate sample size	Population	Opioid	Dose	Administration	Comparison	Duration	Patient setting	Included outcomes
-	NCT02454751	NRT, NB, cross-over	20	CHF	Fentanyl	50 µg	Nebulized	No treatment	Single dose	Outpatient	Secondary: SaO ₂ , RR pre- and post-exercise
-	NCT03018756	RCT, DB, cross-over	20	IPF	Fentanyl	100 µg	Nebulized	Placebo	Single dose	Outpatient	Secondary: RR pre- and post-exercise
MORPHILD	NCT02622022	RCT, DB, parallel	36	ILD	Morphine	20-40 mg/day	Oral	Placebo	One week	Unknown	Secondary: SaO ₂ in rest
MORDYC	NCT02429050	RCT, DB, parallel	124	COPD	Morphine SR	20-30 mg/day	Oral	Placebo	Four weeks	Outpatient	Primary: PaCO ₂ , PaO ₂ , SaO ₂ , RR in rest
DYS-NOC	NCT02801838	NRT, SB, parallel	50	ICU patients	Morphine	10 mg	No data	No treatment	Single or double dose	Inpatient	Secondary: blood gases in rest
BEAMS	NCT02720822	RCT, DB, parallel	171	COPD	Morphine SR	8, 16, 24 or 32 mg	Oral	Placebo	Three weeks	Outpatient	Secondary: PetCO ₂ , SaO ₂ in rest

TABLE S5. Risk of bias of randomized controlled trials

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Other sources of bias
Abernethy, 2003 [16]	+	+	+	+	+	-	-
Allard, 1999 [17]	?	+	+	+	+	+	+
Beauford, 1993 [18]	?	?	+	?	+	-	-
Bruera, 1993 (part 1) [19]	?	?	?	?	+	+	-
Charles, 2008 [20]	+	+	+	+	+	+	-
Chua, 1997 [21]	?	?	+	?	+	+	-
Cuervo Pinna, 2015 [22]	?	?	+	?	+	-	+
Eiser, 1991 (part 1) [23]	?	?	?	?	+	+	-
Eiser, 1991 (part 2) [23]	?	?	?	?	+	+	-
Gamborg, 2013 [24]	?	?	+	?	+	-	+
Grimbert, 2004 [25]	?	+	+	+	+	-	+
Harris-Eze, 1995 [26]	?	+	+	+	+	+	+
Hui, 2014 [27]	+	+	+	+	+	+	-
Jankelson, 1997 [28]	?	+	+	+	+	+	-
Jensen, 2012 [29]	?	+	+	+	-	+	+
Johnson, 2002 [30]	+	+	+	+	+	+	+
Krajnik, 2009 [31]	?	?	-	-	+	-	+
Light, 1989 [32]	?	?	-	-	+	+	-
Light, 1996 [33]	?	?	+	?	+	+	?
Masood, 1995 [34]	?	?	+	?	+	-	+
Mazzocato, 1999 [35]	?	?	+	?	+	+	+
Munck, 1990 (part 2) [36]	?	?	?	?	-	+	+
Natalini, 2011 [37]	+	+	+	+	+	+	+
Navigante, 2010 [38]	+	+	-	-	+	-	+
Nosedá, 1997 [39]	?	?	+	+	+	+	+
Otulana, 2004 (phase 3) [40]	-	-	-	-	?	-	-
Oxberry, 2011 [41]	+	+	+	+	+	+	+
Poole, 1998 [42]	+	+	?	+	+	+	+
Rice, 1987 [43]	+	?	?	?	+	+	+
Robin, 1986 [44]	+	+	-	-	-	+	+
Schonhofer, 1998 [45]	-	-	-	-	-	+	-
Shohrati, 2012 [46]	?	?	+	?	+	+	-
Smith, 2009 [47]	?	?	+	+	-	+	?
Williams, 2003 [48]	?	?	+	+	+	+	-
Woodcock, 1982 [49]	?	?	+	+	-	?	-

+ low risk of bias; - high risk of bias; ? unclear risk of bias.

TABLE S6. Risk of bias of non-randomized trials							
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Other sources of bias
Allcroft, 2013 [50]	–	–	–	–	+	–	+
Boyd, 1997 [51]	–	–	–	–	+	+	+
Bruera, 1990 [52]	–	–	–	–	+	+	+
Bruera, 1993 (part 2) [19]	–	–	–	–	+	+	–
Clemens, 2007 [53]	–	–	–	–	+	+	+
Clemens, 2008.1 [54]	–	–	–	–	+	+	+
Clemens, 2008.2 [55]	–	–	–	–	+	+	+
Clemens, 2008.3 [56]	–	–	–	–	+	+	+
Clemens, 2009 [57]	–	–	–	–	+	+	+
Clemens, 2011 [58]	–	–	–	–	+	+	+
Cohen, 1991 [59]	–	–	–	–	+	+	+
Coyne, 2002 [60]	–	–	–	–	–	+	+
Currow, 2011 [61]	–	–	–	–	+	+	+
Gauna, 2008 [62]	–	–	–	–	+	+	–
Munck, 1990 (part 1) [36]	–	–	–	–	+	–	+
Otulana, 2004 (phase 4) [40]	–	–	–	–	?	–	–
Tanaka, 1999 [63]	–	–	–	–	+	+	–

+ low risk of bias; – high risk of bias; ? unclear risk of bias.

TABLE S7. Risk of bias of prospective observational studies									
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest at start of study	Comparability of cohorts	Assessment of outcome	Length of follow-up	Adequacy of follow-up	Total
Allen, 2005 [1]	★		★	★		★	★	★	6
Hu, 2004 [4]	★		★					★	3
Oxberry, 2013 [7]	★	★					★	★	4
Pang, 2016 [8]	★		★	★			★	★	5

Study	PaCO ₂ (kPa)		PetCO ₂ (kPa)		PaO ₂ (kPa)		SaO ₂ (%)		RR (breaths/minute)		RD number Definition
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	
Abernethy, 2003 [16]	-	-	-	-	-	-	Excluded (no data shown)	-	At rest	I: 20 (5) C: 21 (4)	0
Allard, 1999 [17]	-	-	-	-	-	-	-	-	At rest	O: -1.6 (2.3) ^{1*}	-
Beauford, 1993 [18]	-	-	At rest and on exertion (Emax)	No change (no data shown)	-	-	Excluded (baseline data shown)	-	-	-	-
Bruera, 1993 (part 1) [19]	-	-	-	-	-	-	At rest	I: 92 (2) C: 92 (2)	At rest	I: 24 (8) C: 22 (10)	-
Charles, 2008 [20]	-	-	-	-	-	-	At rest	N: +1.9 (6.1) ¹ S: +0.2 (6.0) ¹ C: +2.1 (3.4) ^{1*}	At rest	N: -3.7 (5.0) ^{1*} S: -4.7 (6.1) ¹ C: -4.2 (4.5) ^{1*}	-
Chua, 1997 [21]	-	-	At rest and on exertion (Bruce), %	R-I: 5.0 (0.5) R-C: 4.6 (0.6) E-I: 5.3 (0.9) E-C: 5.0 (0.9)	-	-	At rest and on exertion (Bruce)	R-I: 99.3 (1.0) [‡] R-C: 100 (0) [‡] E-I: 98.9 (1.4) E-C: 99.5 (0.9)	At rest and on exertion (Bruce)	R-I: 14 R-C: 18 E-I: 23 E-C: 26	-
Cuervo Pinna, 2015 [22]	-	-	-	-	-	-	At rest and on exertion (6MWT)	R-I: 93.2 (3.7) R-C: 93.8 (3.9) E-I: 90.3 (5.6) E-C: 91.5 (6.1)	Excluded (no data shown)	-	-
Eiser, 1991 (part 1) [23]	At rest, arterial	2.5 mg: 5.4 (0.9) 5 mg: 5.0 (0.6) C: 5.2 (0.6)	At rest	2.5 mg: 4.4 (0.9) 5 mg: 4.5 (1.3) C: 4.1 (0.9)	At rest, arterial	2.5 mg: 8.6 (1.3) 5 mg: 9.7 (1.3) C: 9.0 (1.9)	At rest	2.5 mg: 90 (6.3) 5 mg: 89 (6.3) C: 89 (6.3)	-	-	-
Eiser, 1991 (part 2) [23]	At rest, arterial	I: 5.3 (0.3) [†] C: 5.0 (0.3)	-	-	At rest, arterial	I: 8.6 (0.6) [†] C: 9.2 (0.8)	-	-	-	-	-
Gamborg, 2013 [24]	-	-	-	-	-	-	At rest	No change (no data shown)	At rest	No change (no data shown)	0
Grimbert, 2004 [25]	-	-	-	-	-	-	At rest	O: 94.4 (3.3)	At rest	O: 21.2 (8.4)	-
Harris-Eze, 1995 [26]	-	-	On exertion (Emax)	No change (no data shown)	-	-	At rest and on exertion (Emax)	R: no change (no data shown) E-2.5 mg: 85 (7) E-5 mg: 85 (6)	At rest and on exertion (Emax)	R: no change (no data shown) E-2.5 mg: 40 (9) E-5 mg: 43 (11)	-

TABLE S8. Results of randomized controlled trials

Study	PaCO ₂ (kPa)		PetCO ₂ (kPa)		PaO ₂ (kPa)		SaO ₂ (%)		RR (breaths/minute)		RD
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	number Definition
								E-C: 84 (7)		E-C: 40 (12)	
Hui, 2014 [27]	-	-	-	-	-	-	At rest and on exertion (6MWT)	R-I: 96.5 (2.6); -0.6 (1.1) ¹ R-C: 96.2 (1.9); +1.2 (2.1) ¹ E-I: 96.8 (2.4); -1.2 (1.7) ¹ E-C: 96.1 (1.9); +0.8 (2.7) ¹	At rest and on exertion (6MWT)	R-I: 18.2 (1.6); -0.6 (3.3) ¹ R-C: 18.6 (1.6); 0 (1.1) ¹ E-I: 21.0 (2.9); -2.4 (2.7) ^{1*} E-C: 23.4 (3.9); -1.2 (3.9) ¹	-
Jankelson, 1997 [28]	-	-	-	-	-	-	On exertion (6MWT)	20 mg: 87.4 (6.6) 40 mg: 87.6 (6.2) C: 87.2 (4.6)	-	-	-
Jensen, 2012 [29]	-	-	At rest and on exertion (CWRT)	R-I: 4.9 (0.5) R-C: 4.9 (0.6) E-I: 5.8 (1.0) E-C: 5.8 (1.0)	-	-	At rest and on exertion (CWRT)	R-I: 96.3 (1.7) R-C: 96.5 (1.4) E-I: 94.1 (3.1) I-C: 93.4 (6.6)	At rest and on exertion (CWRT)	R-I: 19.7 (4.2) R-C: 20.2 (4.2) E-I: 33.8 (5.5) E-C: 35.1 (4.5)	0
Johnson, 2002 [30]	-	-	-	-	-	-	-	-	At rest	I: 21 (6) C: 21 (6)	-
Krajnik, 2009 [31]	At rest, venous	No change (no data shown)	-	-	At rest, venous	No change (no data shown)	At rest	No change (no data shown)	-	-	-
Light, 1989 [32]	At rest and on exertion (Emax), arterial	R-I: 4.9 (0.9) R-C: 4.7 (0.6) E-I: 5.6 (1.0) E-C: 5.1 (1.1) [‡]	-	-	At rest and on exertion (Emax), arterial	R-I: 10.2 (1.6) R-C: 10.4 (1.9) E-I: 8.9 (1.5) E-C: 9.6 (2.1) [‡]	At rest and on exertion (Emax)	R-I: 93.5 (3.2) R-C: 94.1 (3.1) E-I: 89.9 (6.4) E-C: 91.4 (6.3) [‡]	At rest and on exertion (Emax)	R-I: 19.9 (4.2) R-C: 20.1 (1.7) E-I: 28.0 (4.8) E-C: 31.6 (6.1)	-
Light, 1996 [33]	-	-	On exertion (Emax)	I: +0.1 (0.2) ¹ C: -0.1 (0.2) ¹	-	-	-	-	-	-	-
Masood, 1995 [34]	-	-	-	-	-	-	On exertion (Emax)	O: 93.7 (3.6)	On exertion (Emax)	O: 53.7 (17.4)	-
Mazzocato, 1999 [35]	-	-	-	-	-	-	At rest	I: 0 (1.5) ¹ C: -0.8 (1.3) ¹	At rest	I: -2 (2.2) ¹ C: 0 (1.7) ^{1#}	0 Difference in SaO ₂
Munck, 1990	At rest, arterial	I: +0.2 (-0.3;0.8) ² C: -0.1 (-0.7;1.3) ²	-	-	At rest, arterial	I: -0.4 (-3.9;1.5) ² C: -0.3 (-2.3;1.9) ²	At rest	O: 0 ³	Excluded (no data)	-	-

TABLE S8. Results of randomized controlled trials											
Study	PaCO ₂ (kPa)		PetCO ₂ (kPa)		PaO ₂ (kPa)		SaO ₂ (%)		RR (breaths/minute)		RD
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	number Definition
(part 2) [36]									shown)		
Natalini, 2011 [37]	At rest, arterial	PSV-I: 6.27 (1.9)* PSV-C: 5.9 (1.9)	-	-	At rest, arterial	PSV-I: 14.4 (13.2;19.7) ⁴ ; -0.27 (-2.67;-1.33) ⁵ PSV-C: 12.0 (11.7;13.9) ⁴ ; no cfb data shown	-	-	At rest	PSV-I: 19 (5)*; +8 (4;12) ⁵ PSV-C: 29 (27;30) ⁴ ; no cfb data shown UB-I: 20 (18;23) ⁴ *; +9 (6;13) ⁵ UB-C: 31 (5); no cfb data shown	-
Navigante, 2010 [38]	-	-	-	-	-	-	At rest	FTP-I: 94.1 (3.7) FTP-C: 94.7 (2.9) FUP-I: 94.6 (2.8) FUP-C: 94.6 (3.1)	-	-	-
Nosedá, 1997 [39]	-	-	-	-	-	-	At rest	10mg+O ₂ : 93 (6)* 20mg+O ₂ : 94 (4)* 10mg-O ₂ : 90 (8) C: 95 (4)*	At rest	10mg+O ₂ : 17.9 (5.3) 20mg+O ₂ : 19.1 (4.6) 10mg-O ₂ : 19.0 (3.9) C: 19.1 (3.9)	-
Otulana, 2004 (phase 3) [40]	-	-	-	-	-	-	At rest	No change (no data shown)	At rest	No change (no data shown)	-
Oxberry, 2011 [41]	-	-	-	-	-	-	At rest	1h-mor: -0.5 (1.7) ¹ 1h-oxy: -0.2 (1.5) ¹ 1h-C: -0.6 (1.6) ¹ 4d-mor: -0.7 (2.0) ¹ 4d-oxy: -0.5 (2.0) ¹ 4d-C: -0.3 (1.7) ¹	At rest	1h-mor: -1.1 (1.7) ¹ 1h-oxy: -1.6 (1.6) ¹ 1h-C: -1.1 (2.0) ¹ 4d-mor: -0.5 (2.7) ¹ 4d-oxy: -1.6 (2.5) ¹ 4d-con: -0.9 (2.7) ¹	-
Poole, 1998 [42]	-	-	-	-	-	-	At rest	I: +0.3 (1.5) ¹ C: +0.1 (0.9) ¹	-	-	-
Rice, 1987 [43]	At rest, arterial	24h-I: 5.59 (0.6)* 24h-C: 5.45 (0.3) 1m-I: 5.45 (0.5)* 1m-C: 5.20 (0.8)	-	-	At rest, arterial	4h-I: 7.81 (1.5) 24h-C: 8.65 (1.5) 1m-I: 8.45 (1.5) 1m-C: 7.99 (1.3)	-	-	-	-	-
Robin, 1986 [44]	At rest	No change (no data shown)	-	-	At rest	No change (no data shown)	-	-	-	-	-
Schonhofer, 1998 [45]	At rest, capillary	I: 5.41 (0.6)* [‡] C: 4.88 (0.7)	-	-	At rest, capillary	I: 7.77 (0.7)* [‡] C: 8.24 (0.8)	-	-	-	-	0

TABLE S8. Results of randomized controlled trials											
Study	PaCO ₂ (kPa)		PetCO ₂ (kPa)		PaO ₂ (kPa)		SaO ₂ (%)		RR (breaths/minute)		RD number Definition
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	
Shohrati, 2012 [46]	-	-	-	-	-	-	-	-	At rest	I: -1.5 (1.1) ^{1#} C: -0.1 (0.3) ¹	-
Smith, 2009 [47]	-	-	-	-	-	-	At rest	No change (no data shown)	At rest	No change (no data shown)	-
Williams, 2003 [48]	-	-	On exertion (Emax)	I: 5.2 (1.0) C: 5.1 (0.9)	-	-	-	-	On exertion (Emax)	I: 29 (4) C: 31 (8)	-
Woodcock, 1982 [49]	At rest, arterial	30mg: 4.67 (0.5) [‡] 60mg: 4.77 (0.4) [‡] C: 4.42 (0.4)	-	-	At rest, arterial	30mg: 9.57 (0.7) 60mg: 9.35 (1.0) C: 9.45 (0.6)	-	-	-	-	-

Results are displayed as post-treatment scores + standard deviation are presented, unless stated else.

C: change in control group; cfb: change from baseline; CWRT: constant work rate test; E: measured on exertion; Emax: maximal exercise test; I: change in intervention group; N: change in nebulized group; O: overall change (no specification of change in intervention and control group); PaCO₂: partial pressure of arterial carbon dioxide; PaO₂: partial pressure of arterial oxygen; PetCO₂: partial pressure of end-tidal carbon dioxide; PSV: pressure support ventilation; R: measured at rest; RD: respiratory depression; RR: respiratory rate; S: change in systemic group; SaO₂: arterial oxygen saturation; UB: unassisted breathing.

* significant different change between baseline and post-treatment

[‡] significant difference between post-treatment of intervention and control group

[†] trend for a difference

[#] significant different change between intervention and control group

¹ mean change from baseline + standard deviation

² median change from baseline + range

³ median change from baseline

⁴ median post-treatment score + interquartile range post-treatment scores

⁵ median change from baseline + interquartile range change from baseline

TABLE S9. Results of non-randomized trials											
Study	PaCO ₂ (kPa)		PetCO ₂ (kPa)		PaO ₂ (kPa)		SaO ₂ (%)		RR (breaths/ minute)		RD number Definition
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	
Allcroft, 2013 [50]	-	-	At rest	No change (no data shown)	-	-	Excluded (baseline data only)		-	-	0
Boyd, 1997 [51]	-	-	-	-	-	-	-	-	At rest	0	-
Bruera, 1990 [52]	-	-	At rest	4.40 (1.2)	-	-	At rest	86 (11)	At rest	31 (9)	-
Bruera, 1993 (part 2) [19]	-	-	-	-	-	-	-	-	-	-	0
Clemens, 2007 [53]	-	-	-	-	-	-	At rest	95 (4.0)	At rest	29 (5)*	0
Clemens, 2008.1 [54]	At rest, trans-cutaneous	5.71 (0.7)	-	-	-	-	At rest	93.3 (2.8)	At rest	-29.0 (4.0)*	0 Increase in PaCO ₂
Clemens, 2008.2 [55]	At rest, trans-cutaneous	4.52 (0.8)	-	-	-	-	At rest	94.8 (4.0)	At rest	29.0 (3.1)*	0 Increase in PaCO ₂ >6.0 kPa or ≥0.5 kPa above baseline, decrease in RR < 10 breaths/ minute and decrease in SaO ₂ < 90%
Clemens, 2008.3 [56]	At rest, trans-cutaneous	ON: 4.99 (8.8) PT: 4.52 (1.1)	-	-	-	-	At rest	ON: 95.1 (4.5) PT: 94.3 (3.7)	At rest	ON: 28.0 (3.0)* PT: 28.3 (3.1)*	0 Increase in PaCO ₂ >6.0 kPa or ≥0.5 kPa above baseline, decrease in RR < 10 breaths/ minute and decrease in SaO ₂ < 90%
Clemens, 2009 [57]	At rest, trans-cutaneous	Hypoxic/ON: 5.20 (0.7) Hypoxic/PT: 4.67 (1.2) Non-hypoxic/ON: 5.07 (0.8) Non-hypoxic/	-	-	-	-	At rest	Hypoxic/ON: 91.0 (1.2)* Hypoxic/PT: 87.0 (6.0)* Non-hypoxic/ON: 95.0 (3.5) Non-hypoxic/	At rest	Hypoxic/ON: 24.5 (4.4)* Hypoxic/PT: 26.3 (4.6)* Non-hypoxic/ON: 27.0 (4.0)* Non-hypoxic/	0 Increase in PaCO ₂ >6.0 kPa or ≥0.5 kPa above baseline, decrease in RR < 10 breaths/ minute and decrease in SaO ₂ <

TABLE S9. Results of non-randomized trials											
Study	PaCO ₂ (kPa)		PetCO ₂ (kPa)		PaO ₂ (kPa)		SaO ₂ (%)		RR (breaths/ minute)		RD
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	number Definition
		PT: 4.80 (0.8)						PT: 95.0 (3.0)		PT: 27.0 (3.4)*	90%
Clemens, 2011 [58]	At rest, trans-cutaneous	5.03 (0.7)	-	-	-	-	At rest	95.2 (3.5)	At rest	32.0 (4.0)*	0 Increase in PaCO ₂ >6.0 kPa or ≥0.5 kPa above baseline, decrease in RR < 10 breaths/ minute and decrease in SaO ₂ < 90%
Cohen, 1991 [59]	At rest, unclear place of measurement	Increase (no data shown)	-	-	At rest, unclear place of measurement	Increase in patients with PaO ₂ <8.0 kPa; decrease in patients with PaO ₂ >8.0 kPa (no data shown)	-	-	At rest	Fluctuation in RR; only in 1 patient the RR fell below 10 breaths/ minute (no data shown)	-
Coyne, 2002 [60]	-	-	-	-	-	-	At rest	96.7 (1.2)*	At rest	24.1 (1.7)*	-
Currow, 2011 [61]	-	-	-	-	-	-	-	-	-	-	0
Gauna, 2008 [62]	-	-	-	-	-	-	At rest	95.3 (3.2)	At rest	22.6 (5.5) *	-
Munck, 1990 (part 1) [36]	At rest, arterial	No change (no data shown)	-	-	At rest, arterial	No change (baseline data only)	At rest	SaO ₂ declined temporarily from 93 to 92 after 1 hour on day 2 (120 mg)*	At rest	No change (no data shown)	0
Otulana, 2004 (phase 4) [40]	-	-	-	-	-	-	-	-	At rest	No change (no data shown)	-
Tanaka, 1999 [63]	-	-	-	-	-	-	At rest	No change (no data shown)	At rest	No change (no data shown)	0 Decrease in RR > 10% and reduction of SaO ₂ > 5.

Results are displayed as post-treatment scores + standard deviation are presented, unless stated else.

ON: opioid-naïve; PaCO₂: partial pressure of arterial carbon dioxide; PaO₂: partial pressure of oxygen; PetCO₂: partial pressure of end-tidal carbon dioxide; PT: pre-treated; RD: respiratory depression; RR: respiratory rate; SaO₂: arterial oxygen saturation.

* significant change from baseline

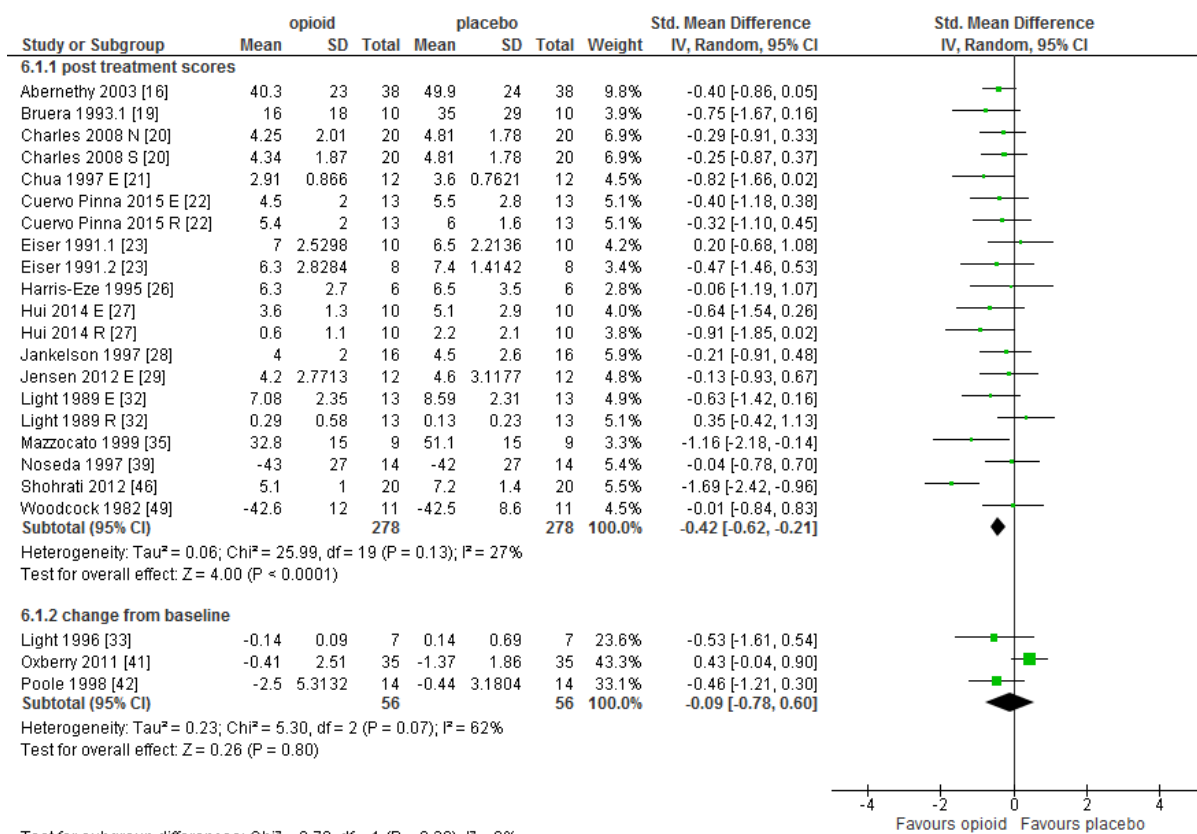


FIGURE S1. Effect of opioid treatment in patients with advanced disease on breathlessness.

E: measured on exertion; N: nebulized administration; R: measured at rest; S: systemic administration.

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