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

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Take home message

There is no evidence for clinically relevant respiratory adverse effects of opioids for chronic breathlessness.

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Abstract

Background: Previous studies have shown that opioids can reduce chronic breathlessness in advanced disease. However, physicians remain reluctant to prescribe opioids for these patients, commonly due to fear of respiratory adverse effects.

Aim: To systematically review reported respiratory adverse effects of opioids in patients with advanced disease and chronic breathlessness.

Methods: Pubmed, Embase, Cochrane central register of controlled trials, CINAHL, ClinicalTrials.gov and the reference lists of relevant systematic reviews were searched. Two independent researchers screened against predefined inclusion criteria and extracted data. Meta-analysis was conducted where possible.

Results: We included 63 out of 1990 articles, describing 67 studies. Meta-analysis showed an increase in partial pressure of carbon dioxide (0.27 kPa; 95% CI 0.08 to 0.45) and no significant change in partial pressure of oxygen and oxygen saturation (both $p>0.05$). Non-serious respiratory depression (definition variable/not stated) was described in 4/1064 patients. One cancer patient pre-treated with morphine for pain needed temporary respiratory support following nebulized morphine for breathlessness (single case study).

Conclusions: We found no evidence of significant or clinically relevant respiratory adverse effects of opioids for chronic breathlessness. Heterogeneity of design and study population, and low study quality are limitations. Larger studies designed to detect respiratory adverse effects are needed.

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Introduction

Breathlessness is defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [1]. Breathlessness is one of the most uncomfortable symptoms in patients with advanced disease [1]. In cancer, 50 to 70% of patients suffer from breathlessness, while in chronic obstructive pulmonary disease (COPD) this prevalence is as much as 56 to 98% [2, 3].

Opioids can reduce chronic breathlessness (breathlessness that persists despite optimal treatment of the underlying pathophysiology and results in disability [4]) in patients with advanced diseases [5-8]. However, while physicians are mostly willing to prescribe opioids for breathlessness in the last days or weeks of life, they are often reluctant to prescribe opioids to those earlier in their disease trajectory [9]. Their main concerns are fear of respiratory adverse effects and lack of evidence-based guidelines [10-12]. Data about respiratory adverse effects of opioids are limited and conflicting. Systematic reviews on effects of opioids on chronic breathlessness in adults with advanced life limiting disease showed no evidence for the following outcomes: respiratory depression, increase in partial pressure of arterial carbon dioxide ($PaCO_2$), increase in partial pressure of end-tidal carbon dioxide ($PetCO_2$), decrease in partial pressure of arterial oxygen (PaO_2) or decrease in arterial oxygen saturation (SaO_2) [5-8]. However, meta-analyses on these outcomes have not been conducted before.

Conversely, observational studies have reported one or more cases of severe respiratory depressions in patients using opioids for breathlessness [13-16]. Most guidelines in palliative care recommend the use of opioids for chronic breathlessness [17-19]. However, guidelines in respiratory medicine, for example the recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [20], are more circumspect because of possible serious adverse events and limited effectiveness. To date there is little evidence whether and to what extent opioids lead to respiratory adverse effects in patients with chronic breathlessness.

The aim of this systematic review and meta-analysis was to study the occurrence of respiratory adverse effects (in particular increase of $PaCO_2$ and $PetCO_2$, decrease of PaO_2 and SaO_2, decrease in respiratory rate (RR), and occurrence of respiratory depression) in patients with advanced disease and chronic breathlessness who are treated with opioids. Respiratory adverse effects are examined in experimental studies, observational studies as well as case reports. However none of the previous reported reviews included all these study types. Therefore, to generate a full overview of the current knowledge, we included experimental studies, observational studies and case reports.

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Methods

A systematic review and meta-analysis was performed according to the Cochrane methodology [21]. Results are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22]. The protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42016033691).

Search strategy

The following databases were searched: PubMed, Embase on Ovid, Cochrane central register of controlled trials and CINAHL on EBSCO (inception date to March 31, 2016). Search terms comprised (dyspnoea OR synonyms) AND (opioid OR synonyms) and included both terms of controlled vocabulary and free search in title and abstract (table S1a-S1d). Furthermore, ClinicalTrials.gov was searched for ongoing or completed studies using the same search terms (May 29, 2017; table S1e). Following de-duplication, we included all original research articles such as randomized controlled trials (RCTs), non-randomized trials, case-control studies, cohort studies, chart reviews, case reports and case studies. Reference lists of three relevant systematic reviews [6-8] were searched by hand and experts in the field were contacted. We included articles in the English, Dutch, German, French and Spanish languages. When a full text article was not accessible, this was requested from the authors.

Study selection

For study screening, we used Endnote X7 (Thomson Reuters, Philadelphia, PA). The titles and abstracts were screened independently by two researchers (CV and either DJ, MvdB or SD) and selected based on the description of treatment for chronic breathlessness using opioids. The remaining full text articles were screened by two researchers (CV and either SD (English), DJ (German or Dutch) or LV (French or Spanish)) against all eligibility criteria: (1) participants included patients, regardless of their primary condition; (2) any opioid as intervention prescribed for breathlessness, regardless of dose or route of prescription; and (3) primary or secondary outcomes included $PaCO_2$, PaO_2, SaO_2, or RR. During the screening process, we decided to also include $PetCO_2$, occurrence of respiratory depression and breathlessness as outcomes. Any type of control group was considered. We excluded studies including only healthy subjects or studies that used an opioid in combination with other treatments and the effect of the opioid could not be distinguished. Consensus was reached by discussion. The study designs of included articles were categorised as follows: RCTs, non-randomized trials (NRTs), prospective observational studies (POSs), retrospective observational studies (ROSs), and case reports (CRs).

Risk of bias

Two researchers independently assessed the risk of bias on the study level (CV and either SD (English), DJ (German) or LV (French)). For the RCTs, we assessed this risk of bias regarding random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting using the Cochrane Risk of Bias tool [21]. The Cochrane Risk of Bias tool was also used to assess the risk of bias in NRTs. Since no control condition was included in these studies, selection bias, performance bias and detection bias were estimated as high risk of bias in all NRTs. For POSs, we assessed the risk of bias regarding selection, comparability and exposure/outcome using the Newcastle-Ottawa Quality Assessment Scale [23]. Consensus was reached by discussion. The risk of bias in ROSs and CRs was not assessed.

Data collection

Data were extracted by two researchers (CV and either SD (English), DJ (German) or LV (French)) using a predefined extraction form in Microsoft Excel, including data on study characteristics (design, duration, setting, in- and exclusion criteria); type of intervention (intervention, comparison, dose, mode and timing of administration); study population (sample size, age, gender, diagnosis, disease severity and use of oxygen); and outcomes (breathlessness; respiratory outcomes: $PaCO_2$, $PetCO_2$, PaO_2, SaO_2, RR and occurrence of respiratory depression; mode of assessment, missing data). When two articles appeared to describe overlapping research questions and study populations, we contacted the authors to provide more information. We recorded the baseline values and change from baseline or post-treatment scores of the respiratory outcomes. When only a description of the change from baseline was given, this was taken into account. The form was piloted on two articles of each study type and adapted as needed.

Data synthesis

Change from baseline measurement scores or post-treatment measurement scores, whichever was reported, were collected for the $PaCO_2$, $PetCO_2$, PaO_2, SaO_2 and RR. For the RCTs, these results were compared between the intervention and control group. For the NRTs, POSs, ROSs and CRs, the change from baseline was examined. Meta-analyses were performed using the results of RCTs; however RCTs without a placebo comparator group were not included. When both a change from baseline and a post-treatment score were reported, the post-treatment score was used in the meta-analyses. Furthermore, the highest dose or latest measurement was included in the meta-analyses if multiple doses of the same opioid or repeated measurements were reported. When an RCT compared more than one opioid with placebo, the morphine group was included in the meta-analysis. For measurements on exertion, the submaximal measures at a fixed time point were

included. To verify if the included RCTs showed a pooled effect of improving breathlessness, meta-analysis on the effect of opioids on breathlessness was performed. These results were presented as standardized mean difference (SMD) + 95% confidence interval (CI), since different scales to measure breathlessness were used. Results of the meta-analyses on $PaCO_2$, $PetCO_2$, PaO_2, SaO_2 and RR were presented as mean difference (MD) + 95% CI, as the same scales to measure comparable outcomes were used. In all meta-analyses a random effects model was used, since the study designs were heterogeneous [21]. Results of PaO_2 and $PaCO_2$ that were reported in mmHg were converted to kPa (1 mmHg = 0.133 kPa).

Some RCTs contributed more than one contrast between the opioid and control group for the same outcome (i.e. subjects were measured multiple times under comparable conditions). To account for this clustering of multiple contrasts within one study sample, we used a multilevel meta-analysis approach to determine if any within-study clustering was present. If there was evidence of within-study clustering, quantified by the intraclass correlation coefficient, the results of the multilevel approach were preferred over the standard approach [24]. To examine the impact of the context of assessment (at rest or on exertion), the number of doses (single dose or multiple doses) or the route of administration (nebulized or systemic), a mixed-effects meta-regression was performed. Subgroup analyses were performed for variables which appeared to be of impact. When no impact appeared, all outcomes were analysed together.

When a study assessed the occurrence of respiratory depression, the frequency of occurrence and the definition used was reported. Analysis of this outcome was descriptive.

Analyses were performed using Review Manager version 5.3 (The Northern Cochrane Centre 2014, Copenhagen, Denmark) and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). GRADEPro Guideline Development Tool (GDT) software was used to construct the Summary of Findings table. Results are shown *per* category of respiratory adverse effect. P-values of 0.05 or lower were considered statistically significant.

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Results

Study characteristics

The search identified 1990 articles, of which 63 met the inclusion criteria (figure 1). The 63 included articles reported on 67 studies: 35 RCTs (table 1), 17 NRTs (table 1), four POSs (table S2), five ROSs (table S2) and six CRs (table S3). Six ongoing studies, four RCTs and two NRTs were identified (table S4). $PaCO_2$, PaO_2 and $PetCO_2$ are examined in one study, SaO_2 is examined in four studies and RR is examined in three studies. In one study, it is not clear which blood gases are examined. In one study the respiratory adverse effects are a primary outcome and in five studies the respiratory adverse effects are secondary outcomes.

Nineteen RCTs were included in the meta-analysis on the effect of opioid treatment on breathlessness [25-42]. Eight RCTs used a visual analogue scale to examine breathlessness [25, 26, 29, 35, 36, 38, 40], six RCTs used the Borg scale [27, 30-34], three RCTs used a numeric rating scale [28, 39, 41], one RCT used the dyspnoea domain of the Chronic Respiratory Questionnaire [42] and one RCT used an oxygen cost diagram [37]. The RCTs that reported post treatment scores showed effectivity of opioids in relieving breathlessness (SMD -0.42; 95% CI -0.62 to -0.21; I^2 27%; Figure S1). The RCTs that reported changes from baseline were not able to show effectivity of opioids in relieving breathlessness (SMD -0.09; 95% CI -0.78 to 0.60; I^2 62%; Figure S1).

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Table 1. Patient characteristics, study design and included outcomes of included randomized controlled trials and non-randomized trials

Study	Design	N (% men)	Population (n)	Mean age (SD) (*yr*)	Opioid	Dose	Administration	Comparison	Duration	Patient setting	Included outcomes
Abernethy, 2003 [25]	Cross-over	48 (73)	COPD (42) Cancer (3) MND (1) RLD (2)	76 (5)	Morphine SR	20 mg/day	Oral	Placebo	4 days	Outpatient	SaO_2, RR, RD
Allard, 1999 [43]	Parallel	33 (42)	Cancer (33)	63.3	Based on current treatment[1]	50% of current dose[1]	Oral or parenteral	25% of current dose[1]	Single dose	Inpatient	RR
Beauford, 1993 [44]	Cross-over	8 (88)	COPD (8)	60.8 (9.1)	Morphine	1, 4 or 10 mg	Nebulized	Placebo	Single dose	Outpatient	$PetCO_2$
Bruera, 1993 (part 1) [26]	Cross-over	10 (-)	Cancer (10)	No data	Morphine	Target: 150% of current dose (34±12 mg)	Parenteral	Placebo	Single dose	Inpatient	SaO_2, RR
Charles, 2008 [38]	Cross-over	20 (55)	Cancer (20)	69 (range 48-83)	Hydro-morphone[1,2]	5 mg	Nebulized	Placebo[2]	Single dose	Inpatient/ outpatient	SaO_2, RR
Chua, 1997 [27]	Cross-over	12 (100)	CHF (12)	65.5 (1.5)	Dihydro-codeine	1 mg/kg body weight (77.4 ± 3.1 kg)	Oral	Placebo	Single dose	Unclear	$PetCO_2$, SaO_2, RR
Cuervo Pinna, 2015 [28]	Cross-over	13 (85)	Cancer (13)	65.2 (10.4)	Fentanyl	Opioid-naïve: 200 µg Pre-treated: 400 µg	Oral	Placebo	Single dose	Unclear	SaO_2, RR
Eiser, 1991 (part 1) [29]	Cross-over	14 (57)	COPD (14)	65 (range 49-79)	Diamorphine	10 or 20 mg/day	Oral	Placebo	2 weeks	Outpatient	$PaCO_2$, $PetCO_2$, PaO_2, SaO_2
Eiser, 1991 (part 2) [29]	Cross-over	10 (60)	COPD (10)	65 (range 49-79)	Diamorphine	15 mg/day	Oral	Placebo	1 day	Outpatient	$PaCO_2$, PaO_2
Gamborg, 2013 [45]	Parallel	20 (10)	Cancer (20)	Median 69 (range 42-84)	Morphine	Target: 1/12 of total daily dose with a maximum of 24 mg) (median 8.2%)	Oral	Subcutaneous morphine; 60% of 1/12 of total daily dose with a maximum of 14.4 mg)	Single dose	Inpatient	SaO_2, RR, RD
Grimbert,	Cross-over	12 (92)	Cancer (12)	63 (range 44-	Morphine	120 mg/day	Nebulized	Placebo	2 days	Inpatient	SaO_2, RR

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Study	Design	N (% men)	Population (n)	Mean age (SD) (*yr*)	Opioid	Dose	Administration	Comparison	Duration	Patient setting	Included outcomes
2004 [46]				82)							
Harris-Eze, 1995 [30]	Cross-over	6 (83)	ILD (6)	49 (16)	Morphine	Target: 2.5 mg (mean 1.9 mg) or 5 mg (mean 3.7 mg)	Nebulized	Placebo	Single dose	Outpatient	$PetCO_2$, SaO_2
Hui, 2014 [39]	Parallel	20 (45)	Cancer (20)	55 (range 27-75)	Fentanyl[3]	30-350 µg[4]	Parenteral	Placebo	Single dose	Outpatient	SaO_2, RR
Jankelson, 1997 [31]	Cross-over	16 (69)	COPD (16)	69 (range 61-85)	Morphine	20 or 40 mg	Nebulized	Placebo	Single dose	Inpatient	SaO_2
Jensen, 2012 [32]	Cross-over	16 (58)	COPD (16)	70.5 (2.3)	Fentanyl	50 µg	Nebulized	Placebo	Single dose	Unclear	$PetCO_2$, SaO_2, RR, RD
Johnson, 2002 [47]	Cross-over	10 (100)	CHF (10)	67 (range 45-85)	Morphine	10-20 mg/day	Oral	Placebo	4 days	Inpatient	$PaCO_2$, PaO_2, SaO_2, RR
Krajnik, 2009 [48]	Parallel	10 (40)	Cancer (10)	55.5 (range 39-73)	Morphine	5 mg	Nebulized	2 types of nebulization	Single dose	Inpatient	$PaCO_2$, PaO_2, SaO_2
Light, 1989 [33]	Cross-over	13 (100)	COPD (13)	65.9 (range 58-70)	Morphine	0.8 mg/kg	Oral	Placebo	Single dose	Unclear	$PaCO_2$, PaO_2, SaO_2, RR
Light, 1996 [34]	Cross-over	7 (100)	COPD (7)	66.4 (3.3)	Morphine	30 mg	Oral	Placebo	Single dose	Unclear	$PetCO_2$
Masood, 1995 [49]	Cross-over	12 (100)	COPD (12)	66.3 (7.0)	Morphine	N: 10 and 25 mg P: 1 and 2.5 mg	Nebulized and parenteral	Placebo	Single dose	Inpatient	SaO_2, RR
Mazzocato, 1999 [40]	Cross-over	9 (66)	Cancer (9)	73 (range 66-83)	Morphine	5 mg (or 150% of pre-treatment dose)	Parenteral	Placebo	Single dose	Inpatient	SaO_2, RR, RD
Munck, 1990 (part 2) [50]	Cross-over	21 (-)	COPD (21)	Median 67 (range 50-78)	Codeine	60 mg/day	Oral	1 gram paracetamol	7 days	Inpatient	$PaCO_2$, PaO_2, SaO_2, RR
Natalini, 2011 [51]	Cross-over	13 (43)	Trauma (3) COPD (3) Pneumonia (3) Stroke (2)	Median 78 (IQR 73-82)	Remifentanyl	0.05 µg/kg/min	Parenteral	Placebo	Single dose	Inpatient	$PaCO_2$, PaO_2, RR

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Table 1. Patient characteristics, study design and included outcomes of included randomized controlled trials and non-randomized trials

Study	Design	N (% men)	Population (n)	Mean age (SD) (*yr*)	Opioid	Dose	Administration	Comparison	Duration	Patient setting	Included outcomes
			Epilepsy (1) Peritonitis (1)								
Navigante, 2010 [52]	Parallel	63 (-)	Cancer (31)	Median 55 (range 30-80)	Morphine[1]	22.5 (4.12) mg	Oral	Midazolam	5 days	Outpatient	SaO_2
Noseda, 1997 [35]	Cross-over	17 (76)	COPD (12) IPF (1) Cancer (3) CHF (1)	69 (11)	Morphine	10 or 20 mg	Nebulized	Placebo	Single dose	Inpatient	SaO_2, RR
Otulana, 2004 (phase 3) [53]	Cross-over	19 (-)	Asthma (19)	Range 19-64	Morphine	2.2, 4.4 or 8.8 mg	Nebulized	3 doses	Single dose	Unclear	RR
Oxberry, 2011 [41]	Cross-over	35 (86)	CHF (35)	70.2 (11.1)	Morphine Oxycodone	20 mg/day 10 mg/day	Oral	Placebo	4 days	Outpatient	SaO_2, RR
Poole, 1998 [42]	Cross-over	16 (69)	COPD (16)	70.7 (6.4)	Morphine SR	Target: 40 mg (mean 25 mg)	Oral	Placebo	6 weeks	Outpatient	SaO_2
Rice, 1987 [54]	Cross-over	11 (100)	COPD (11)	Range 59-79	Codeine	120 mg	Oral	Promethazine	1 month	Unclear	$PaCO_2$, PaO_2
Robin, 1986[5] [55]	Cross-over	1 (0)	OLD	63	Hydro-morphone	12 mg/day	Rectal	Placebo	24 hours	Outpatient	$PaCO_2$, PaO_2
Schonhofer, 1998 [56]	Cross-over	20 (55)	Lung emphysema (20)	68.5 (6.8)	Morphine SR	Target: 90 mg (mean 49 mg)	Oral	Usual care	10 days	Inpatient	$PaCO_2$, PaO_2, RD
Shohrati, 2012 [36]	Parallel	40 (100)	COPD (40)	No data	Morphine	1 mg/day	Nebulized	Placebo	5 days	Inpatient	RR
Smith, 2009 [57]	Cross-over	2 (0)	Cancer (1) Unclear (1)	49 & 59	Fentanyl	25 µg	Nebulized	Placebo	Single dose	Inpatient	SaO_2, RR
Williams, 2003 [58]	Cross-over	16 (94)	CHF (16)	61 (8.8)	Diamorphine	1 or 2 mg	Parenteral	Placebo	Single dose	Unclear	$PetCO_2$, RR
Woodcock, 1982 [37]	Cross-over	16 (-)	COPD (16)	No data	Dihydro-codeine	90 or 180 mg/day	Oral	Placebo	2 weeks	Outpatient	$PaCO_2$, PaO_2
Allcroft, 2013 [59]	Non-randomized	13 (62)	COPD (13)	Median 78 (range 68-89)	Morphine	10 mg/day	Oral	-	4 days	Inpatient/ outpatient	$PetCO_2$, SaO_2, RR, RD

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Study	Design	N (% men)	Population (n)	Mean age (SD) (*yr*)	Opioid	Dose	Administration	Comparison	Duration	Patient setting	Included outcomes
Boyd, 1997 [60]	Non-randomized	15 (47)	Cancer (15)	73 (range 62-85)	Morphine	20 mg/day or 130% of pre-treatment dose	Oral	-	7-10 days	Inpatient/ outpatient	RR
Bruera, 1990 [61]	Non-randomized	20 (55)	Cancer (20)	64 (17)	Morphine	5 mg or 2.5 times pre-treatment dose	Parenteral	-	Single dose	Inpatient	$PetCO_2$, SaO_2, RR
Bruera, 1993 (part 2) [26]	Non-randomized	45 (-)	Cancer (45)	No data	Morphine[3]	Same dose as for pain treatment	Parenteral	-	Total of 312 doses	Unclear	RD
Clemens, 2007 [62]	Non-randomized	25 (44)	Cancer (25)	65.5 (15.1)	Morphine[6] Hydro-morphone[6]	8.2 (7.5) mg MED 19.5 (1.8) mg MED	No data	-	Single dose	Inpatient	SaO_2, RR, RD
Clemens, 2008.1 [63]	Non-randomized	6 (67)	ALS (6)	57.0 (6.9)	Morphine[1]	6.3 (7.0) mg	Oral	-	Single dose	Inpatient	$PaCO_2$, SaO_2, RR, RD
Clemens, 2008.2 [64]	Non-randomized	14 (57)	Cancer (14)	Median 67 (range 40-84)	Hydro-morphone[1]	2.5 (1.8) mg	Oral	-	Single dose	Inpatient	$PaCO_2$, SaO_2, RR, RD
Clemens, 2008.3 [65]	Non-randomized	27 (48)	Cancer (25) ALS (2)	Range 40-90	Morphine[1,6] Hydro-morphone[1,6]	2.5-20.0 mg 0.5-6.0 mg	Oral	-	Single dose	Inpatient	$PaCO_2$, SaO_2, RR, RD
Clemens, 2009 [66]	Non-randomized	46 (54)	Cancer (46)	Range 40-90	Morphine[1,6] Hydro-morphone[1,6]	2.5-20 mg 1-6 mg	Oral	-	Single dose	Inpatient	$PaCO_2$, SaO_2, RR, RD
Clemens, 2011 [67]	Non-randomized	26 (54)	Cancer (26)	66.0 (13.6)	Morphine[1] Hydro-morphone[1]	8.4 (7.2) mg 4 (4.7) mg	Oral	-	Single dose	Inpatient	$PaCO_2$, SaO_2, RR, RD
Cohen, 1991 [68]	Non-randomized	8 (-)	Cancer (8)	61.9 (range 50-79)	Morphine[1]	120 mg/day	Parenteral	-	60 hours	Unclear	$PaCO_2$, PaO_2, RR
Coyne, 2002 [69]	Non-randomized	35 (43)	Cancer (33) Pulmonary embolism (1) AIDS (1)	56	Fentanyl	25 µg	Nebulized	-	Single dose	Inpatient	SaO_2, RR
Currow,	Non-	83 (64)	COPD (45)	74.6 (9.1)	Morphine	Target: 10-30 mg	Oral	-	Target 3	Outpatient	RD

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Study	Design	N (% men)	Population (n)	Mean age (SD) (*yr*)	Opioid	Dose	Administration	Comparison	Duration	Patient setting	Included outcomes
2011 [70]	randomized		Cancer (24) ILD (10) Other (4)			Phase II: 16.5 (8) mg Phase IV: 14.0 (6.3) mg			months (mean 142 days)		
Gauna, 2008 [71]	Non-randomized	4 (50)	COPD and PF (2) Cancer (2)	Range 52-85	Fentanyl[3]	200-400 µg	Oral	-	Single dose	Inpatient	SaO_2, RR
Munck, 1990 (part 1) [50]	Non-randomized	21 (-)	COPD (21)	Median 67 (range 50-78)	Codeine	60 and 120 mg	Oral	-	Single dose	Outpatient	$PaCO_2$, PaO_2, SaO_2, RR, RD
Otulana, 2004 (phase 4) [53]	Non-randomized	6 (-)	Asthma (6)	No data	Morphine	17.6 mg	Nebulized	-	Single dose	Unclear	RR
Tanaka, 1999 [72]	Non-randomized	15 (53)	Cancer (15)	Median 61 (range 42-76)	Morphine	20 mg	Nebulized	-	Single dose	Inpatient	SaO_2, RR, RD

ALS: amyotrophic lateral sclerosis; CHF = congestive heart failure; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; IQR = interquartile range; MND: motor neuron disease; OLD = obstructive lung disease; $PaCO_2$: partial pressure of arterial carbon dioxide; PaO_2: partial pressure of arterial oxygen; $PetCO_2$: partial pressure of end-tidal carbon dioxide; PF: pulmonary fibrosis; RD: respiratory depressions; RLD: restrictive lung disease; RR: respiratory rate; SaO_2: arterial oxygen saturation; SD = standard deviation

[1] application of opioid for breakthrough breathlessness possible

[2] application of placebo for breakthrough breathlessness possible

[3] intervention prescribed for breakthrough breathlessness

[4] Based on dose of current opioids for breakthrough breathlessness

[5] This study is a single-patient RCT, which was terminated after the run in phase and the placebo arm. Data are therefore based on the run-in arm.

[6] choice of dose or type of opioid depended on general condition of the patient

Risk of bias

As shown in table S5, the risk of bias of the RCTs was estimated as low risk or unclear risk in most studies. Other sources of bias were assessed as high in 43% of the studies, mainly because of the absence of a wash-out period in cross-over trials. Table S6 shows the risk of bias of the NRTs. Selection bias, performance bias and detection bias were estimated as high risk of bias, as no control condition was included in these studies. In the other categories, the risk of bias was assessed as low in most studies. The POSs were graded with three to six out of eight stars due to comparability and representativeness of cohorts (table S7).

Effect on outcomes of respiratory adverse effects

The effect of opioid treatment on outcomes of respiratory adverse effects is shown in tables S2, S3, S8 and S9. A summary of the effects of the RCTs included in the meta-analyses is presented in the Summary of Findings table (table 2). Since none of the intraclass correlation coefficients of comparisons within RCTs were significantly different from 0 and therefore the effect of clustering on the outcomes was negligible for RCTs that contributed more than one contrast for a single outcome measure, the results are analysed using regular meta-analyses instead of three-level meta-analyses. Most of the included RCTs were cross-over trials and we included both parallel and cross-over trials in the meta-analyses together. Results of 12 RCTs could not be included in the meta-analyses because they compared opioid treatment to other than placebo (treatment with another substance [50, 52, 54], another dose or route of administration [43, 45, 48, 53], or usual care [56] [Table S8]). Results of 7 RCTs could not be included in the meta-analyses because they reported their outcomes as median scores [51], did not report the outcomes *per* treatment arm [46, 49], or reported the outcome only in qualitative wording [30, 44, 55, 57] (Table S8).

Effect on $PaCO_2$

The effect of opioid treatment on $PaCO_2$ was assessed in nine RCTs [29, 33, 37, 50, 51, 54-56], five of which could be included in the meta-analysis [29, 33, 37, 51]. The meta-analysis showed that treatment with opioids increased $PaCO_2$ (MD 0.27; 95% CI 0.08 to 0.45; I^2 0%, see figure 2a). The meta-regression revealed no influence from the context of assessment (p=0.437; however there was only one RCT during exercise) or the number of doses (p=0.507) on the $PaCO_2$. Route of administration was not taken into account, since all RCTs administered the opioid systemically.

One RCT examined the effect of opioids on $PaCO_2$ during exercise [33]. The difference between the intervention and control group after administration of morphine was statistically significant at maximal exercise (5.8 and 5.1 kPa respectively, p<0.001). The effect on $PaCO_2$ was also assessed in seven NRTs [50, 63-68]. One NRT found a significant increase in $PaCO_2$ [68]. Finally, the effect on

$PaCO_2$ was assessed in one ROS [73] and one CR describing two cases [74]. In both studies the opioids were nebulized. The opioids were prescribed as single dose or up to 15 days. In all studies, $PaCO_2$ was measured at rest. None of these studies showed a significant effect of opioid treatment on $PaCO_2$.

Effect on $PetCO_2$

The effect of opioid treatment on $PetCO_2$ was assessed in seven RCTs [27, 29, 30, 32, 34, 44, 58], five of which could be included in the meta-analysis [27, 29, 32, 34, 58]. The meta-analysis showed a non-significant increase of the $PetCO_2$ (MD 0.13; 95% CI -0.02 to 0.27; I^2 0%, see figure 2b). The RCT by Light *et al.* [34] had a low variance compared to the other studies and consequently a high weight in the analysis. Therefore, the meta-analysis was repeated, but with weighing based on the sample size. The effect on $PetCO_2$ was still not significant (MD 0.13; 95% CI -0.11 to 0.37; I^2 0%). The meta-regression revealed no influence from the context of assessment (p=0.375), the number of doses (p=0.679) or the route of administration (p=0.473) on the $PetCO_2$.

The effect on $PetCO_2$ was also assessed in two NRTs [59, 61]. These studies reported no significant change in $PetCO_2$ [59, 61].

- insert figure 2 about here -

Effect on PaO_2

The effect of opioid treatment on PaO_2 was assessed in nine RCTs [29, 33, 37, 50, 51, 54-56], four of which could be included in the meta-analysis [29, 33, 37]. The meta-analysis showed a non-significant decrease of the PaO_2 (MD -0.26; 95% CI -0.68 to 0.15; I^2 0%, see figure 3a). The meta-regression revealed no influence from the context of assessment (p=0.420; however only one RCT during exercise) or the number of doses (p=0.815) on the PaO_2. Route of administration was not taken into account, since all RCTs administered the opioid systemically.

One RCT examined the effect of opioids on PaO_2 during exercise [33]. The difference between the intervention and control group after administration of morphine was statistically significant at maximal exercise (8.8 and 9.6 kPa respectively, $p<0.05$). The effect on PaO_2 was also assessed in two NRTs [50, 68]. One NRT found a significant decrease in PaO_2 [68]. Finally, the effect on PaO_2 was assessed in one CR describing two cases [74]. In this study the opioids were nebulized for up to 15 days. PaO_2 was measured in rest. This study showed no significant effect of opioid treatment on PaO_2.

Effect on SaO_2

The effect of opioid treatment on SaO_2 was assessed in 24 RCTs [25-33, 35, 38-42, 44-46, 48-50, 52, 53, 57], 14 of which could be included in the meta-analysis [26-33, 35, 38-42]. The meta-analysis showed that SaO_2 decreased after opioid use (MD -0.41; 95% CI -0.73 to -0.08; I^2 0%, see figure 3b). The RCT by Chua *et al.* [27] was the only RCT showing a significant difference in SaO_2 between the intervention and control group at rest (99.3% and 100% respectively, P=0.03). This RCT reported a variance of 0 in the control group in rest and consequently had a high weight in the analysis. Therefore, as a sensitivity analysis the meta-analysis was repeated, but with weighing based on the sample size. The effect on SaO_2 was no longer significant (MD -0.31; 95% CI -1.06 to 0.45; I^2 0%). The meta-regression revealed no influence from the context of assessment (p=0.730), the number of doses (p=0.165) or the route of administration (p=0.538) on the SaO_2.

Furthermore, the effect of opioids on SaO_2 was assessed in 12 NRTs [50, 59, 61-67, 69, 71, 72]. One NRT showed a significant decrease in SaO_2 from 93 to 92% [50] after a single dose of 120 mg codeine. However, this decrease was temporary and not clinically relevant. Finally, the effect of opioids on SaO_2 was assessed in two POSs [75, 76], two ROSs [73, 77] and three CRs describing seven cases [74, 78, 79]. In these studies the opioids were administered systemically (n=3), nebulized (n=2) or *via* unknown route (n=1). The opioids were prescribed as single dose or as repeated doses up to three months. In all studies, SaO_2 was measured at rest. None of these studies showed a significant effect of opioid treatment on SaO_2. In two RCTs [25, 44] and one NRT [59] SaO_2 was measured, but no outcome data were reported.

Effect on RR

The effect of opioid treatment on RR was assessed in 23 RCTs [25-28, 30, 32, 33, 35, 36, 38-41, 43, 45-47, 49-51, 53, 57, 58], 13 of which could be included in the meta-analysis [25, 26, 30, 32, 33, 35, 36, 38-41, 47, 58]. The meta-analysis showed that treatment with opioids significantly decreased the RR (MD -1.10; 95% CI -1.49 to -0.71; I^2 0%, see figure 3c). The RCT by Shohrati *et al.* [36] was the only RCT showing a significant difference in change in RR between the intervention and control group (-1.5 and -0.1 respectively, P<0.001). This RCT had a low variance compared to the other studies and consequently a high weight in the analysis. Therefore, the meta-analysis was repeated, but with weighing based on the sample size. The effect on RR was no longer significant (MD -0.58; 95% CI -1.72 to 0.56; I^2 0%). The heterogeneity among the RCTs describing post-treatment scores was 0%. The meta-regression revealed no influence from the context of assessment (p=0.496), the number of doses (p=0.904) or the route of administration (p=0.139) on the RR.

The effect on RR was also assessed in 15 NRTs [50, 53, 59-69, 71, 72]. These studies also showed that opioids caused no significant change in RR. Finally, the effect on RR was assessed in three POSs [75, 76, 80], two ROSs [73, 77] and four CRs describing ten cases [74, 78, 79, 81]. In these studies the

opioids were administered systemically (n=4), nebulized (n=4) or *via* unknown route (n=1). The opioids were prescribed as single dose or as repeated doses up to three months. In all studies, SaO_2 was measured at rest. These studies also showed that opioids caused no significant change in RR. In two RCTs [28, 50] and one NRT [50], RR was measured, but no outcome data were reported.

- insert figure 3 about here -

Occurrence of respiratory depression

The occurrence of respiratory depressions was reported in five RCTs [25, 32, 40, 45, 56], eleven NRTs [26, 50, 59, 62-67, 70, 72], two POSs [14, 75], three ROSs [15, 82, 83] and four CRs describing ten cases [13, 74, 79, 84]. Of these 25 studies, eleven studies defined respiratory depression [13, 14, 40, 63-67, 72, 75, 84]. Definitions were based on an increase in $PaCO_2$ of >0.5 kPa or to more than 6.0 kPa, a decrease in RR of >10% or to less than 10 breaths/minute and a decrease in SaO_2 of >5% or to less than 90%. Hu *et al.* [14] observed a case of respiratory depression (defined as decrease in RR to <10 breaths/minute) in one patient with terminal cancer both at the beginning of the POS and two days prior to death. Kawabata *et al.* [15] reported three patients experiencing a respiratory depression (no definition given), which were not serious. It was not stated if these patients were treated for pain or breathlessness. Lang and Jedeikin [13] described a case of respiratory depression (defined as RR of 4-5 breaths/minute, very poor respiratory effort and minimal wheezing over both lung fields) after administration of 4 mg nebulized morphine and 4 mg dexamethasone for breakthrough breathlessness in a patient already using 10 mg oral slow-release morphine three times *per* day and 10 mg oral immediate release morphine when required for cancer-related pain.

Quality of the evidence

The quality of the evidence was assessed as very low to moderate for the different outcomes (table 2). Only RCTs were included in this assessment. For all outcomes, the majority of the RCTs were small with insufficient power to assess respiratory adverse events and the quality was therefore downgraded. Furthermore, limitations in the design and implementation were observed. In several RCTs, patients who were pre-treated with opioids were included, which had a negative effect on the quality of the evidence. Finally, only a small number of RCTs included assessment of $PaCO_2$ and PaO_2.

Table 2. Summary of findings

Opioids compared to placebo for patients with chronic breathlessness due to advanced disease

Patient or population: patients with chronic breathlessness due to advanced disease
Setting: inpatient and outpatient setting
Intervention: opioids
Comparison: placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with opioids**				
$PaCO_2$	The mean $PaCO_2$ ranged from **4.4 to 5.9** kPa	The mean $PaCO_2$ in the intervention group was 0.27 kPa higher (0.08 kPa higher to 0.45 kPa higher)	-	146 (5 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	
$PetCO_2$: PTS	The mean $PetCO_2$: PTS ranged from **4.13 to 5.79** kPa	The mean $PetCO_2$: PTS in the intervention group was 0.10 kPa higher (0.13 kPa lower to 0.34 kPa higher)	-	156 (4 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	
$PetCO_2$: CFB	The mean $PetCO_2$: CFB was -**0.05** kPa	The mean $PetCO_2$: CFB in the intervention group was 0.14 kPa higher (0.05 kPa lower to 0.33 kPa higher)	-	14 (1 RCT)	⊕⊕◯◯ LOW [b,c]	
PaO_2	The mean PaO_2 ranged from **9.0 to 10.4** kPa	The mean PaO_2 in the intervention group was 0.26 kPa lower (0.68 kPa lower to 0.15 kPa higher)	-	118 (4 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	
SaO_2: PTS	The mean SaO_2: PTS ranged from **84 to 100** %	The mean SaO_2: PTS in the intervention group was 0.47 % lower (0.87% lower to 0.07% lower)	-	312 (10 RCTs)	⊕◯◯◯ VERY LOW [a,b,d]	
SaO_2: CFB	The mean SaO_2: CFB ranged from **-0.3 to 2.1** %	The mean SaO_2: CFB in the intervention group was 0.29 % lower (0.85% lower to 0.26% higher)	-	196 (4 RCTs)	⊕⊕◯◯ LOW [b,c]	
RR: PTS	The mean RR: PTS ranged from **18.6 to 40.0**	The mean RR: PTS in the intervention group was 0.86 lower (1.71 lower to 0.02 lower)	-	328 (9 RCTs)	⊕◯◯◯ VERY LOW [a,b,d]	
RR: CFB	The mean RR: CFB ranged from **-4.2 to 0.0**	The mean RR: CFB in the intervention group was 0.80 lower (1.83 lower to 0.24 higher)	-	208 (4 RCTs)	⊕◯◯◯ VERY LOW [b,c,d]	

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Table 2. Summary of findings

Opioids compared to placebo for patients with chronic breathlessness due to advanced disease

Patient or population: patients with chronic breathlessness due to advanced disease
Setting: inpatient and outpatient setting
Intervention: opioids
Comparison: placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with opioids**				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CFB: change from baseline; **CI:** Confidence interval; **MD:** Mean difference; **PTS:** post-treatment scores

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. There were limitations in design and implementation, which suggest a risk of bias
b. The majority of studies were not powered to detect changes in this outcome
c. A small amount of studies included
d. Patients who were pre-treated with opioids were included

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Discussion

Main findings

This systematic review on occurrence of respiratory adverse effects following opioid treatment for breathlessness shows a great heterogeneity of treatment regimens and patient populations. Given this heterogeneity, we found no evidence that clinically relevant respiratory adverse effects are to be expected in patients with breathlessness who are treated with opioids, while included studies confirmed previous reports of opioid-related benefit for breathlessness. This suggests that clinicians' fears of respiratory obtundation with the use of low dose opioids seem to be unfounded.

The meta-analysis showed an increase in $PaCO_2$ of 0.27 kPa (0.09 to 0.46). Although this increase is statistically significant, it is not considered to be clinically relevant [85]. Indeed, the pooled mean (SD) $PaCO_2$ was 5.35 (1.08) kPa, so the mean difference in $PaCO_2$ was only 25% of the SD. However, few RCTs reported on $PaCO_2$ and the quality of this evidence is assessed as very low. One NRT reported a significant deterioration of blood gases, but the participants received 120 mg parenteral morphine *per* day [68]. Given that 20% to 40% of oral morphine is bioavailable, this represents a much higher dose than the oral morphine doses required in the dose titration study (10-30 mg oral morphine *per* day) [70] or the oral morphine repeat dose trials (20 mg oral morphine *per* day) [25, 41, 47]. The meta-analyses showed a significant decrease in SaO_2 of 0.41% (0.73 to 0.08) and RR of 1.10 times/minute (1.49 to 0.71). However, in both analyses one study had a high weighting due to a small variance. The statistical significance disappeared when the analyses were repeated weighted on sample size. In four cases, a diagnosis of respiratory depression was made during the study, but the definition was poorly stated. In three occasions the indication and dose were not clear [15]. In the fourth case, respiratory depression occurred in a patient with advanced metastatic cancer pre-treated with opioids. The additive effect of both treatments, leading to a high dose of morphine, may have led to respiratory depression [13]. It is notable that no cases of respiratory depression were noted in the context of RCTs, with their close monitoring. Neither the meta-analyses of $PetCO_2$, PaO_2, SaO_2 and RR nor the studies that were not included in the meta-analyses showed a significant deterioration of these outcomes. The meta-regression did not provide a significant effect for the context of assessment (at rest or on exertion), the number of doses (single dose or multiple doses) or the route of administration (nebulized or systemic), which is surprising especially for the route of administration. Previous reviews have reported a different effect of opioids on breathlessness when administered systemically or nebulized [5, 6]. The results of this meta-regression might be related to small effects within the included studies and the fact that only six studies included in the meta-analysis used nebulized opioid.

Six ongoing studies were identified. Three of them only examine a single or double dose of opioids and are therefore not able to say anything about the long-term effect. Of the three other studies, two have respiratory adverse effects as a secondary outcome and the sample size calculation will therefore probably not be based on this outcome. Only the MORDYC study primary focusses on respiratory adverse effects and based the sample size calculation on the $PaCO_2$ [85]. This study will add valuable information about the occurrence of respiratory adverse effects.

Our findings are consistent with other reviews on opioids for chronic breathlessness [5, 6, 86] and episodic breathlessness [87]. These reviews included RCTs [5, 6, 86, 87], NRTs [6, 86] and CRs [87]. The authors of these reviews also found no clinically relevant effect on blood gases or oxygen saturation, or respiratory depression after treatment with different types of opioids in patients with advanced disease. In hypoxic patients with cancer, an improvement of SaO_2 was reported [6]. However, these reviews only included 39 studies and meta-analyses could not be performed due to limited results on respiratory adverse effects. Furthermore, the focus of these reviews was on the effect of opioid treatment on breathlessness and search terms for respiratory adverse effects were not included.

Limitations of the included studies

First, the risk of bias of the included studies was often difficult to estimate. The outcomes of interest in the current review were secondary outcomes in the majority of the included studies and therefore the method of outcome assessment was often not described. The method of randomization or allocation concealment was inadequately described in most studies. Since it was difficult to score the risk of bias and to set a cut-off point, we did not include a sensitivity analysis including only the studies with a low risk of bias. *Second*, there was great heterogeneity in the dosing regimens and comparators used. The prescribed doses ranged between the studies, with eight studies prescribing high doses of opioids. In 34 experimental studies, one observational study and seven cases, only a single dose of opioids was prescribed, so the long-term effect was not assessed. Seven RCTs did not include a placebo group, but used different doses, other medication or usual care as comparator. *Third*, the patient populations were heterogeneous. In some studies patients had to be opioid-naïve, but not in others – where patients could continue opioids for pain or where the dose of the study medication was based on current analgesic treatment. *Fourth*, the included studies had a small sample size. The experimental studies included one to 83 participants with only six studies including a sample size of 30 or more participants *per* treatment group. These studies included outcomes of respiratory adverse effects, but were underpowered to properly assess a change in these outcomes. The observational studies used larger sample sizes, but only a proportion of these patients received opioids for breathlessness. In some studies, the results accounted for the entire group, making it

impossible to draw conclusions for the subgroup of our interest. *Fifth*, the definition of respiratory depression differed between studies. The most reliable assessment of respiratory depression is based on the PaO_2 and $PaCO_2$. Measurement of SaO_2 is less reliable [88]. Some authors included RR as a measure of respiratory depression, because this is easier to estimate. Only eleven studies defined respiratory depression and eight used a decrease in SaO_2 as part of the definition. Only four also included an increase of $PaCO_2$. *Finally*, five studies mentioned the assessment of respiratory outcomes in their method section, but didn't include the results (n=3) or only reported the baseline data (n=2). Furthermore, 25 studies reported on the occurrence of respiratory depression but only nine of them mentioned the assessment of respiratory depression in their methods section. Therefore, it is not known if a respiratory depression occurred in one of the remaining 42 studies.

Strengths and limitations of the current review

Our study has several strengths. We included several study types; although RCTs yield the most reliable evidence, observational studies and CRs are closer to daily clinical practice. Furthermore, we included studies that were published in five languages. Because of the large number of included studies, we were able to present the current knowledge of six different outcomes of respiratory adverse effects and were able to perform meta-analyses on five. This provides an overall estimate of the effect of opioid treatment on these outcomes.

Our review also has several limitations. *First*, we only searched four databases. Due to publication bias, we might have failed to identify negative results. However, we also searched one trial register, sought expert opinions and hand-searched the reference lists of important reviews in the field of opioid treatment for chronic breathlessness. We identified a large number of studies, decreasing the chance that we missed important studies. *Second*, several RCTs could not be included in the meta-analyses because of reasons as discussed before. *Third*, we combined results from studies with different contexts of assessment, different number of doses and different route of administration; however, this was done only after the meta-regression which did not yield evidence that these moderators had an effect on the outcome. The number of studies used for this analysis was in some cases very low, making the power to detect effects questionable. However, due to the robustness of the results (i.e. no single moderator was significant in any of the analyses), we combined all measures to be pooled. *Fourth*, the patient populations were too diverse to specify the results for different populations. We primarily expect that patients with COPD and chronic respiratory failure are more at risk for respiratory adverse effects than for example patients with cancer or heart failure. Most of the studies included patients with a specified primary diagnosis (n=54), of which 16 studies only included patients with COPD. However, from these populations it is not known which patients experienced chronic respiratory failure. *Fifth,* we used the Cochrane Risk of Bias tool to assess the

risk of bias in RCTs and NRTs. This tool is designed to use in RCTs, but there was no appropriate alternative to use in NRTs. After assessment of the risk of bias was completed, the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool was published [89]. This might have been a better tool to assess the risk of bias in NRTs and can be used in future studies. *Finally*, we included both cross-over trials and parallel trials in the meta-analysis together and analysed the cross-over trials as if they were parallel trials. This might result in a unit of analysis error, leading to an underweighting of the cross-over trials. Since only two studies included in the meta-analyses of SaO_2 and RR were parallel trials and the remaining studies were cross-over trials, we assume this influence to be negligible.

Implications for clinical practice and future research

Patients are willing to consider opioid treatment for chronic breathlessness, despite the occurrence of adverse effects, and report improvement of quality of life and relief of breathlessness as their main reasons [12]. However, physicians remain reluctant to prescribe opioids for chronic breathlessness, among other things because of fear of adverse clinical outcomes [9-12]. A recent large observational study of older adults with COPD by Vozoris *et al.* [90] showed an association between new prescription of opioid and a small, but statistically significant increase in 30 day mortality and emergency visits. However, palliative care patients (and thus those who form the main group for whom opioids would be prescribed for breathlessness) were excluded and other differences between patients with and without opioid use might explain these findings. In contrast, a registry study of people with advanced COPD on long-term oxygen therapy, with four years follow up, found no association with either hospital admission or survival in people taking 30 mg or less of oral morphine *per* day [91].

This review has shown that the current evidence on respiratory adverse effects of opioid treatment in chronic breathlessness is inconsistent and heterogenic. Only one serious episode of respiratory depression is described, and that in the context of high dose opioids. Based on the evidence included in this review, low dose opioids can be considered as safe treatment for chronic breathlessness in the context of good clinical care and appropriate monitoring. However, the studies that have been conducted are mostly of low quality, short duration and not designed to assess the effect of low dose opioids on respiratory adverse effects. A long term, well-powered randomized controlled trial, like the MORDYC study, is needed. Moreover, including a common respiratory outcome set in all trials of opioids for breathlessness, so that a more robust synthesis could be conducted, is recommended.

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