Harms of Morphine for Chronic Breathlessness in Relation to Dose, Duration and Titration Phase

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Abstract

Context. Morphine to treat severe chronic breathlessness might increase adverse events (AEs).

Objectives. We aimed to evaluate the risk of AEs in relation to dose, duration and titration phase of regular, low-dose sustained-release (SR) oral morphine for chronic breathlessness in people with chronic obstructive pulmonary disease (COPD).

Methods. Secondary analysis of a double-blind, randomized, trial of SR morphine titrated to 0−32 mg/day over three weeks in people with COPD and chronic breathlessness. Risk of AEs by morphine or placebo dose, duration and titration phase (initiation, stable dose or up-titration) was analyzed using multivariable generalized estimating equation (GEE) models.

Results. We included 156 people (49% female) of whom 100 (64%) experienced any AE during week 1: 64% of those on 8 mg/morphine/day; 78% on 16 mg/morphine/day; and 48% on placebo. In multivariable analysis, the AE risk was highest the first week of morphine treatment and decreased in week two (adjusted rate ratio [aRR] 0.71; 95% confidence interval (CI) 0.54, 0.94) and week three (aRR 0.49; 95% CI 0.37, 0.67). Over the three weeks, the AE risk was similar between titration phases, and there was no statistically significant trend with higher morphine doses (*P*-values>0.10). Most AEs did not require treatment discontinuation or dose reduction and resolved by the end of titration.

Conclusion. In people with COPD and severe chronic breathlessness, the risk of AEs was highest during the first week of treatment in a dose-related fashion but did not differ by titration phase or by dose of once-daily SR morphine between 8 and 32 mg/day.

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Key Words

Opioids, breathlessness, COPD, adverse events, randomized controlled trial, placebo controlled trial

Key Message

In a blinded, randomized trial of 156 people with chronic obstructive pulmonary disease (COPD) and chronic breathlessness, morphine increased the risk of adverse events during the first week of treatment but there was no statistically significant difference by titration phase or morphine dose (0−32mg/day). These adverse events were almost always managed without treatment cessation.

Introduction

Breathlessness is the subjective experience of uncomfortable breathing.[1] Chronic breathlessness refers to breathing discomfort that persists despite optimal treatment of the underlying cause and leads to disability.[2,3] This distressing symptom is common in cardiorespiratory conditions such as chronic obstructive pulmonary disease (COPD).

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Treatment with regular, low-dose, sustained-release (SR) morphine has been recommended by a number of guidelines for the symptomatic reduction of chronic breathlessness in people with COPD.[4] However, the evidence for net clinical effect of morphine for chronic breathlessness is conflicting.[5-10] A meta-analysis supported that opioids such as morphine could safely offer symptom relief in steady state.[11] A subsequent, larger randomised clinical trial (RCT) found an improvement with morphine, compared to placebo, in disease-specific health status in patients with COPD without serious adverse effects.[12]

However, the recent BEAMS trial found that SR morphine titrated (in a double-blind, placebo-controlled fashion) between 0− 32 mg/day over three weeks in patients with COPD improved neither the primary outcome of *worst breathlessness* in the previous 24 hours after one week, nor any secondary outcome, but that morphine increased the risk of AEs.[6] The AEs included constipation, somnolence and dizziness, but also serious AEs.[6] Clinicians report fear of adverse events with morphine as a major barrier to symptomatic treatment for breathlessness, particularly in people with COPD.[13]

Knowledge about the longer-term safety profile (over weeks) of SR morphine is scarce. Data are limited on which factors influence the risks of morphine-related AEs, and no study to date has evaluated the risks of AEs in relation to morphine dose, duration, and treatment phase (morphine initiation, stable dose, or up-titration) when given with the aim to reduce symptomatic chronic breathlessness in people with COPD. This knowledge is important as it could enable more tailored symptomatic treatment with morphine in people with severe chronic breathlessness to minimize the risks of AEs and improve people's well-being. The aim of this secondary analysis was to evaluate the risk of AEs in relation to treatment dose, duration, and titration phase (initiation, stable dose and up-titration).

Materials and Methods

Study Design

This study was a secondary analysis of a phase III, multisite, randomized, double-blind, placebo-controlled, dose-increment study of regular, low-dose, oral SR morphine for chronic breathlessness in people with COPD. The details regarding design and randomizations are presented in the BEAMS (Breathless Exertion and Morphine Sulfate) efficacy article.[14] Briefly, participants were randomized at baseline to one of the three arms for week one (once-daily placebo, 8 mg/day or 16 mg/day SR morphine); for weeks two and three, either placebo or an additional SR morphine 8 mg/day was added to the previous dose. In the third week, morphine doses were zero (placebo), eight, 16, 24 or 32 mg per day, with a 1/12 chance of taking a placebo throughout (Fig. 1). There was an optional six-month blinded extension phase in which participants continued taking the allocated treatment which they were prescribed for week three of the protocol, the final blinded titration week. All participants took either a placebo laxative (for the placebo group) or a laxative (for the morphine groups; docusate with sennosides ii

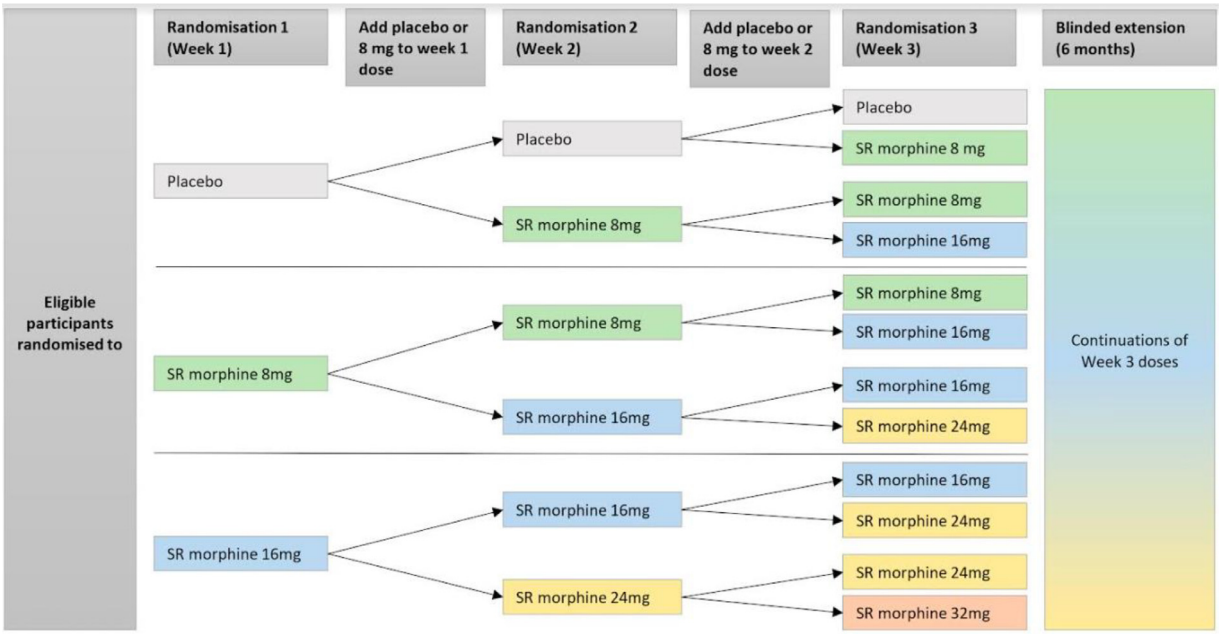

Fig. 1. Randomized titrated dose of extended-release morphine or placebo by trial week.

tablets daily), as well as additional open-label laxatives as needed, to reduce morphine-related constipation.

Ethical Considerations

The study protocol was approved by the Hunter New England Human Research Ethics Committee (Reference 15/12/16/3.06) and by the local research governance offices at each site. The BEAMS trial was prospectively registered (NCT02720822). All participants provided written, informed consent. The study was conducted and reported in accordance with Good Clinical Practice and CONSORT guidelines.

Eligibility Criteria

Inclusion criteria were: age 18 years or older; diagnosed COPD with a post bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio of <0.70; stable medications for COPD; breathlessness defined as modified Medical Research Council (mMRC) breathlessness scale score of 3 or 4 (corresponding to patient statements of "I stop for breath after walking about 100 yards or after a few minutes on the level," "I am too breathless to leave the house," or "I am breathless when dressing"); *worst breathlessness intensity* in the previous 24 hours scoring ≥3 on a 0−10 numerical rating scale (NRS) at baseline; optimised treatment of COPD and any other comorbid causes contributing to chronic breathlessness as confirmed by the responsible clinician; and English-speaking with sufficient reading and writing ability to understand the study measures and procedures.

Exclusion criteria were: treatment with any opioid for breathlessness in the previous seven days or taking of opioid medications during the previous week at an oral morphine equivalent dose of 8 mg/day or greater; pregnant or breastfeeding; a history of adverse reactions to any of the study medications or constituents in the placebo, documented central hypoventilation syndrome, uncontrolled nausea, vomiting or evidence of a gastrointestinal tract obstruction; an Australia−modified Karnofsky performance score (AKPS) less than 50 at baseline;[15] a respiratory or cardiac event in the previous one week (excluding upper respiratory tract infections); evidence of respiratory depression with resting respiratory rate <8/min; current or recent history of abuse of alcohol or substance misuse; renal dysfunction with a calculated creatinine clearance of <20 ml/min; or evidence of severe hepatic impairment as defined by transaminase or bilirubin levels >4-fold normal (excluding Gilbert's syndrome).

Assessments

AEs were recorded at the baseline assessment, in participants' daily diaries in the initiation and titration phase and then with monthly phone calls in the long-term, blinded extension covering during the entire intervention period (including the randomization period and the optional blinded extension). The National Cancer Institute Common Terminology Criteria for AEs version 4 (NCI CTCAEv4) were used for regular reporting of AEs. If a recorded event had appeared or worsened after baseline, then it was counted as an AE. An AE was classified as serious if it had a CTCAE grade of ≥3 or had been otherwise documented as a serious AE as part of trial pharmacovigilance reporting.

A daily patient diary actively sought symptoms that may be related to morphine, such as constipation, anxiety, drowsiness, nausea, vomiting, difficulties thinking clearly, issues passing urine, itching or lack of appetite, for the two baseline days and the three-week randomization phase. These were rated on a Likert scale of 0−3 (corresponding to patient statements of "none", "mild", "moderate" or "severe"). Symptoms that ce caused by morphine were identified beforehand in the literature and recorded in the patient diary; these were also identified in the NCI CTCAEv4 reporting as AEs of special interest.

Potential adverse effects on the respiratory system were assessed using SAE (serious adverse events) clinical data including respiratory rate, pulse oximetry and end-tidal carbon dioxide ($ETCO_2$). Data on AEs were categorized as resolved, change in grade, ongoing at end of study, death, or unknown, and whether withdrawal of the research participant had occurred along with the occurrence of the event.

Of note, SAEs are defined by the outcome (hospitalization, introduction of additional tests or therapies, death) not the blinded investigator's assessment of the SAEs any relationship to the participant's therapy nor the clinical assessment of the event.

Statistical Analyses

All statistical analyses were planned and performed in collaboration with a biostatistician (SC). The study data were analyzed based on randomization group and included all participants who received at least one dose of the randomized treatment. Baseline characteristics were tabulated by randomized treatment group at week three. AEs were tabulated by treatment week, dose and phase, and SAEs were tabulated by treatment phase, dose at the time of the event, event grade and blinded clinician-attributed relationship to therapy.

- Analysis of AEs were divided according to three variables: dose, week (one, two, and three), and treatment phase. Treatment phases were:
  - Treatment initiation: included weeks in which participants were receiving morphine (8 or 16 mg) for the first time;
  - Steady-state: weeks in which participants kept taking the same dose as the week before;

Table 1
Baseline characteristics.

Characteristic	Total	Experienced any adverse event in week one	
		Yes	No
N	156	100	56
Age (yrs) m, mean (SD); median (IQR)	72.0 (8.7); 72.0 (67.0, 78.0)	72.2 (8.7); 72.0 (67.0, 78.0)	71.7 (8.7); 73.0 (66.3, 76.8)
Female	75 (48.1)	49 (49.0)	26 (46.4)
Body mass index (kg/m^2), mean (SD); median (IQR)	27.2 (6.9); 26.3 (22.2, 31.4)	27.2 (7.2); 26.1 (22.0, 31.1)	27.1 (6.4); 26.3 (22.9, 33.0)
Smoking status			
Never smoker	4 (2.6)	2 (2.0)	2 (3.6)
Former smoker	124 (79.5)	78 (78.0)	46 (82.1)
Current smoker	28 (18.0)	20 (20.0)	8 (14.3)
mMRC breathlessness rating			
3	121 (77.6)	76 (76.0)	45 (80.4)
4	35 (22.4)	24 (24.0)	11 (19.7)
Treatment allocation for week one[a]			
0 (row percentage)	50 (32.1)	25 (25.0) (50)	25 (44.6) (50)
8 (row percentage)	55 (35.3)	35 (35.0) (63.6)	20 (35.7) (36.4)
16 (row percentage)	51 (32.7)	40 (40.0) (78.4)	11 (19.6) (21.6)

[a]$P = 0.01$.IQR = interquartile range; mMRC = modified Medical Research Council breathlessness scale; SD = standard deviation.

- Up-titration (increased dose): included all time periods in which participants were up-titrating their morphine dose (from 8 mg/day to 16 mg/day, from 16mg/day to 24 mg/day, or from 24 to 32 mg); and
- Placebo: included all time periods in which participants were taking placebo.

To account for the substantial positive skewness and clustering present in the AE count data, generalized estimating equations (GEEs) with negative binomial distribution and log link function were used to analyze the risk of AEs in relation to morphine dose, duration (week one, two, and three), and titration phase (initiation, steady dose, up-titration or placebo). Considering observed collinearity between dose and titration phase, these factors were also analyzed separately. The analyses were limited to weeks one−three to ensure the consistent classification of AE data into the treatment phase, and AEs during the extension phase and SAEs across the whole study were reported descriptively. Regression models were performed unadjusted, and adjusted for all key factors (baseline age, sex, mMRC breathlessness rating, Australia-modified Karnofsky Performance Scale score, and the Charlson Comorbidity Index (CCI)).[15,16] An exchangeable correlation structure was used to account for study-stage clustering. The robust variance estimators (the Huber-White sandwich estimator of variance) were used to produce consistent point estimates and standard errors.[17]

Results

Participants and Treatment Groups

A total of 156 participants were randomized during week one to the treatment groups: morphine 8 mg/day ($n = 55$), 16 mg/day ($n = 51$), or placebo ($n = 50$). Baseline characteristics of participants are shown in Table 1. Participants who encountered any adverse events during the first week had a mean age of 72 years, 49% were female, and reported a mMRC breathlessness rating of 3 (76%) or 4 (24%). Baseline characteristics were similar between the final randomized treatment groups (Supplementary Table 1).

Adverse Events

During week 1, the proportion of people with at least one AE increased with higher morphine doses (Table 2): placebo (50%), morphine 8 mg/day (64%), and 16 mg/day (78%) ($P = 0.003$ for trend). Compared with people without any AE, people who experienced any AE during week 1 (100/156; 64.1%) had similar baseline age, sex, BMI, and smoking status (Table 1).

During week 2, the proportion of participants with at least one AE was between 48% and 55% across the treatment groups (Table S2). During week three, at least one AE occurred in 39% of those with morphine 8 mg/day, 42% with 16 mg/day, 57% with 24 mg/day, and 44% with 32 mg/day, compared with 50% in the placebo group (Supplementary Table 2).

AEs by treatment week and titration phase are shown in Supplementary Table 3. Initiating morphine was related to higher risk of any AE, compared with placebo, during week 1 (71% for initiation versus 50% for placebo) but with lower risk at week two (32% versus 54%) and more similar risk at week three (36% versus 30%; Supplementary Table 3). Constipation, together with fatigue, nausea and somnolence were the most common AEs during the treatment weeks (Supplementary Table 4−6).

Serious adverse events (SAEs) throughout all blinded phases occurred in 39/156 people (25.0%) who experienced 43 separate SAEs. Only two of these people were on placebo at the time of their SAE. In the

Table 2
Adverse events by study week and morphine dose / placebo.

	Allocated morphine dose				
Study week	Morphine 8 mg/day	Morphine 16 mg/day	Morphine 24 mg/day	Morphine 32 mg/day	Placebo
Week 1	35/55 (63.6%)	40/51 (78.4%)	–	–	25/50 (50.0%)
Week 2	22/46 (47.8%)	21/44 (47.7%)	11/22 (50.0%)	–	13/24 (54.2%)
Week 3	12/31 (38.7%)	16/38 (42.1%)	17/30 (56.7%)	4/9 (44.4%)	6/12 (50.0%)
Extension	14/21 (66.7%)	20/27 (74.1%)	18/22 (81.8%)	6/8 (75.0%)	6/7 (85.7%)

Number (percentage) of participants experiencing at least one adverse event by study week and allocated morphine dose.

Table 3
Serious Adverse events by week and titration phase up to the end of week 3 (initiation and titration phases).

	Titration phase			
Treatment week and dose	Steady dose number of SAEs/subjects	Increased dose number of SAEs/subjects	Initiation number of SAEs/subjects	Placebo number of SAEs/subjects
Week 1	$n = 0$	$n = 0$	$n = 106$	$n = 50$
Placebo	–	–	–	–
8 mg/day	–	–	2/2	–
16 mg/day	–	–	6/6	–
Week 2	$n = 45$	$n = 45$	$n = 22$	$n = 24$
Placebo	–	–	–	–
8 mg/day	2/2	–	2/2	–
16 mg/day	–	–	–	–
24 mg/day	–	2/2	–	–
Week 3	$n = 45$	$n = 52$	$n = 11$	$n = 12$
Placebo	–	–	–	1/1
8 mg/day	1/1	–	1/1	–
16 mg/day	–	4/4	–	–
24 mg/day	–	1/1	–	–
32 mg/day	–	–	–	–

SAE = serious adverse events.

first three weeks of the study during initiation and titration, 22 people had 22 SAEs. (Table 3). NCI CTCAE severity ranged from grades 1 to 5. The majority of events were 'unrelated' in the attribution and none was attributed as 'definite' by the still-blinded investigator at the time of each event. SAEs included increased breathlessness, infections, and two events that met the NCI CTCAEv4 criteria for respiratory failure (both in the morphine group).

There were two people whose SAEs were categorized as "respiratory failure" in the NCI CTCAE nomenclature. One was a 69-year-old participant with severe COPD who was intubated within 18 hours of the first dose of medication with a lower respiratory tract infection that subsequently resolved. The other was a 73-year-old participant with decreasing mobility and increasing shortness of breath and decreasing mobility in the blinded extension phase of the study who was admitted to hospital with an acute coronary syndrome and elevated troponin on a background history of known ischaemic heart disease. Both were assessed by the blinded investigator as unrelated with grades four and three respectively.

Overall, most AEs resolved during the study (77% of AEs in week one, and 76% of those in week two; Table 2) and the number of patients who withdrew due to unacceptable AEs tended to be higher with higher morphine doses but were overall low (Table 4).

Multivariable Risk Analysis

Regression analyses of the risk of AEs in relation to treatment week, dose and titration phase are shown in Table 4. When each factor was analyzed separately without any adjustment, the AE risk was highest during the first week of treatment and decreased during week two (rate ratio [RR] 0.75 versus week one; [95% CI] 0.58,

Table 4
Withdrawals (over total number of participants) due to unacceptable adverse events by study week and morphine dose.

Study week	Morphine 8 mg/day	Morphine 16 mg/day	Morphine 24 mg/day	Morphine 32 mg/day	Placebo
Week 1	2/55 (3.6%)	5/51 (9.8%)	-	-	1/50 (2.0%)
Week 2	1/46 (2.2%)	3/44 (6.8%)	2/22 (9.1%)		1/24 (4.2%)
Week 3	1/31 (3.2%)	1/38 (2.6%)	4/30 (13.3%)	0/9 (0%)	0/12 (0%)

Table 5
Risk of AEs in relation to treatment week, dose and phase.

	Crude RR (95% CI)	*P*-value	Adjusted RR (95% CI)	*P*-value	Adjusted RR (95% CI)	*P*-value
Treatment week						
1	1 *(Ref)*	-	1 *(Ref)*	-	1 *(Ref)*	-
2	0.75 (0.58, 0.97)	0.03	0.71 (0.54, 0.94)	0.02	0.73 (0.52, 1.02)	0.06
3	0.54 (0.42, 0.70)	<0.001	0.49 (0.37, 0.67)	<0.001	0.54 (0.37, 0.79)	<0.001
Morphine dose, mg/day						
0	1.46 (0.94, 2.28)	0.09	1.17 (0.78, 1.75)	0.45		
8	1 *(Ref)*	-	1 *(Ref)*	-		
16	1.25 (0.93, 1.69)	0.14	1.28 (0.96, 1.72)	0.10		
24	0.91 (0.57, 1.45)	0.69	1.40 (0.90, 2.19)	0.13		
32	0.77 (0.42, 1.43)	0.41	1.48 (0.80, 2.75)	0.21		
Titration phase						
Dose initiation	1 *(Ref)*	-			1 *(Ref)*	-
Placebo	1.14 (0.73, 1.81)	0.56			1.06 (0.71, 1.58)	0.78
Steady dose	0.75 (0.53, 1.08)	0.12			1.07 (0.70, 1.65)	0.76
Dose up-titration	0.61 (0.44, 0.84)	0.003			0.92 (0.61, 1.38)	0.68

Associations in terms of rate ratios (RRs) for the number of experienced AEs in relation to treatment week, morphine dose, and titration phase analyzed using generalized estimating equation regression models. To avoid collinearity between the factors, separate models were performed.
1) Each factor analyzed separately without any adjustment.
2) Treatment week and morphine dose analyzed concurrently, adjusted for confounders.
3) Treatment week and titration phase analyzed concurrently, adjusted for confounders. Confounders adjusted for were baseline values of age, sex, modified MRC breathlessness scale score, Australia-modified Karnofsky Performance Scale score, and Charlson Comorbidity Index.
A higher RR reflects increased risk compared with the reference category; for example, RR 1.20 reflects a 20% higher risk of AE compared with the reference category for that variable.
AE = adverse event; CI = confidence interval; Ref = reference category; RR = rate ratio.

0.97) and week 3 (RR 0.54; 0.42, 0.70). The decreased risk of AE after the first week remained after also controlling for morphine dose and treatment phase. In contrast, there was no statistically significant difference in AE risk by morphine dose, neither in crude or adjusted analysis (Table 5). For titration phase, there were no differences by titration phase after adjusting for confounders and treatment duration.

Discussion

In this analysis of a large RCT of double-blinded up-titrated doses of SR morphine compared to placebo for chronic breathlessness in people with COPD, the risk of AEs was independently increased during the first week of treatment (and lower in the subsequent week two and three) where a dose-response association was seen with higher AE risk with higher morphine doses. However, there was no statistically significant difference across the three treatment weeks by morphine dose (in the range 0−32 mg/day) or titration phase after controlling for confounders and treatment duration. Most AEs resolved during the study and <10% of participants had to withdraw from the treatment due to unacceptable AEs.

To the author's knowledge, this is the first study examining the *concurrent impact* on the AE risk of treatment duration, dose, and titration phase of SR morphine for breathlessness in the setting of a placebo-controlled study. The present findings are in line with previous reports that SR morphine 20 mg/day was not related to increased harms compared with placebo in a trial over one week,[18] and that morphine in the present dose range was not found to cause serious adverse events in a meta-analysis of previous smaller trials.[19]

Strengths and Limitations

A strength is that the present analysis is based on standardized longitudinal assessment of AEs during a RCT, according to Good Clinical Practice, where the opioid dose was up-titrated in a double-blinded and placebo-controlled fashion over three weeks, which enabled comparison of risks in relation to doses between 0 (placebo), and morphine at eight, 16, 24, and 32 mg/day, as well as treatment duration and titration phase. Participants were not permitted to use morphine "as needed" during the trial, and outcomes including the prevalence and severity of AEs were evaluated using validated instruments and scales.[20] The GEE analysis could evaluate associations for several factors concurrently, accounting for the other factors in the model as well as potential confounders.

Limitations include that the number of patients decreased over the weeks, due to severe underlying illnesses, with relatively few participants in each group after three weeks. According to the study design, the chances of being on the placebo arm for all three weeks were only one in 12 (identical to the 32 mg/day arm), which might increase the risk of a type II error. Doses were not clearly limited to a specific week or time-period. Instead, different participants could take the same dose in different weeks, which could also correspond to different study phases (i.e., dose initiation, up-titration or steady state). This overlap between the factors may have influenced the findings.

Implications

These findings inform the safety profile of low-dose SR morphine (up to 32 mg/day) for treatment of breathlessness in people with COPD.

For the clinician, the finding that the AE risk was higher in the first week of treatment, in a dose-response fashion, supports that when given morphine should be initiated in a low dose during the first week and should not be titrated more rapidly than weekly.[21] It is also important with prophylactic management against expected effects such as constipation. For patients where the dose could be held stable or up-titrated from the first week, the risk of AEs decreased in the subsequent weeks, highlighting the importance of individualized titration. When given in this way, the present findings provide reassurance that, besides well-known side effects that need to be treated and that most often resolve over time, with treatment or with adjustment of the morphine dose, morphine has an acceptable safety profile also when given for breathlessness in patients with COPD.

Weighing the benefits and harms, the clinician and patient can decide whether to recommend or continue the medication, to change the dose or to discontinue the treatment. Research is needed to delineate further risk factors of AEs to inform which patients are more likely to receive a net benefit from the treatment.

In conclusion, the risk of AEs was highest during the first week of treatment in a dose-related fashion but over three weeks was not greater than placebo for morphine doses 8−32 mg/day for chronic breathlessness in people with COPD.

Author Contributions

DCC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Study concept and design: ME, DF, DCC, MJJ; Acquisition of the data: DF and DCC; Drafting of the manuscript: FA, ME; Critical revision of the manuscript for important intellectual content and approval of the final version: All authors; Statistical analysis: SC.

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Supplementary Table 1

Baseline characteristics according to randomized treatment group for week three.

Characteristic	Treatment group by study week three[b]				
	Morphine 8 mg/day	Morphine 16 mg/day	Morphine 24 mg/day	Morphine 32 mg/day	Placebo
N	39	52	40	12	13
Age, yrs	71.1 (8.2)	72.3 (8.9)	71.9 (9.7)	75.0 (5.9)	71.3 (8.2)
Female	20 (51%)	22 (42%)	20 (50%)	7 (58%)	6 (46%)
Body mass index, kg/m^2	27.4 (8.3)	26.8 (5.9)	27.4 (7.0)	27.7 (5.1)	27.6 (7.8)
Smoking status					
Never smoker	1 (2.6%)	1 (1.9%)	1 (2.5%)	1 (8%)	0 (0%)
Former smoker	30 (77%)	40 (77%)	34 (85%)	10 (83%)	10 (77%)
Current smoker	8 (21%)	11 (21%)	5 (13%)	1 (8%)	3 (23%)
mMRC breathlessness rating[c]					
3	30 (77%)	40 (77%)	33 (83%)	10 (83%)	8 (62%)
4	9 (23%)	12 (23%)	7 (18%)	2 (17%)	5 (39%)
Charlson comorbidity index					
0	20 (51%)	25 (48%)	12 (30%)	3 (25%)	4 (31%)
1–2	13 (33%)	20 (38%)	17 (43%)	9 (75%)	4 (31%)
≥3	6 (15%)	7 (14%)	11 (27%)	0 (0%)	5 (39%)
Comorbidities					
People with at least one other cause of breathlessness (46%)	17 (44%)	21 (40%)	24 (60%)	5 (42%)	6
Asthma (15%)	6 (15%)	5 (10%)	3 (8%)	2 (17%)	2
Bronchiectasis	1 (3%)	1 (2%)	2 (5%)	0 (0%)	0 (0%)
Contributing infective problems	1 (3%)	1 (2%)	0 (0%)	0 (0%)	1 (8%)
Heart failure	6 (15%)	11 (21%)	9 (23%)	2 (17%)	1 (8%)
Lungcancer - known secondary	0 (0%)	0 (0.0%)	0 (0%)	0 (0%)	1 (8%)
Lungcancer - primary	0 (0%)	1 (2%)	1 (3%)	0 (0%)	1 (8%)
Restrictive lung disease	1 (3%)	2 (4%)	5 (13%)	0 (0%)	1 (8%)
Thrombo-embolic cause	2 (5%)	1 (2%)	3 (8%)	1 (8%)	0 (0%)
Other	10 (26%)	6 (12%)	12 (30%)	1 (8%)	1 (8%)

[b]- end of week 3 in the double-blind dose increment period.
[c]mMRC - modified Medical Research Council breathlessness scale.

Supplementary Table 2

Adverse events by study week and morphine dose/placebo.

Study week	Allocated morphine dose				
	Morphine 8 mg/day	Morphine 16 mg/day	Morphine 24 mg/day	Morphine 32 mg/day	Placebo
Week 1	35/55 (63.6%)	40/51 (78.4%)	–	–	25/50 (50.0%)
Week 2	22/46 (47.8%)	21/44 (47.7%)	11/22 (50.0%)	–	13/24 (54.2%)
Week 3	12/31 (38.7%)	16/38 (42.1%)	17/30 (56.7%)	4/9 (44.4%)	6/12 (50.0%)
Extension	14/21 (66.7%)	20/27 (74.1%)	18/22 (81.8%)	6/8 (75.0%)	6/7 (85.7%)

Number (percentage) of participants experiencing at least one adverse event by study week and allocated morphine dose.

Supplementary Table S3

Adverse events by study week, morphine dose, and titration phase.

Treatment week and dose	Steady dose number of AEs/subjects	Increased dose number of AEs/subjects s	Initiated number of AEs/subjects	Placebo number of AEs/subjects
Week 1	$n = 0$	$n = 0$	$n = 106$	$n = 50$
Placebo	–	–	–	81/25
8 mg/day	–	–	74/35	–
16 mg/day	–	–	127/40	–
Week 2	$n = 45$	$n = 45$	$n = 22$	$n = 24$
Placebo	–	–	–	47/13
8 mg/day	35/15	–	15/7	–
16 mg/day	34/13	23/9	–	–
24 mg/day	–	27/11	–	–
Week 3	$n = 45$	$n = 52$	$n = 11$	$n = 20$
Placebo	–	–	–	15/6
8 mg/day	10/8	–	10/4	–
16 mg/day	18/6	17/10	–	–
24 mg/day	15/5	18/12	–	–
32 mg/day	–	7/4	–	–

AE = adverse event.

Supplementary Table 4

Most common adverse events during week one by treatment group.

AEs during week one	Morphine 8 mg/day ($n = 55$) number of AEs/subjects	Morphine 16 mg/day ($n = 51$) number of AEs/subjects	Placebo ($n = 50$) Number of AEs/subjects
Constipation	16/15	17/17	5/4
Fatigue	3/3	10/10	1/1
Nausea	6/6	9/9	8/5
Somnolence	2/2	9/9	6/6
Anorexia	6/6	–	–

Supplementary Table 5

Most common adverse events during week two by treatment group.

AEs during week two	Morphine 8 mg/day ($n = 46$) number of AEs/subjects	Morphine 16 mg/day ($n = 45$) number of AEs/subjects	Morphine 24 mg/day ($n = 21$) number of AEs/subjects	Placebo ($n = 24$) number of AEs/subjects
Somnolence	3/3	0/0	6/6	6/5
Constipation	2/2	10/9	5/5	3/3
Nausea	5/5	4/4	0/0	1/1
Headache	0/0	2/2	0/0	5/5

Supplementary Table 6

Most common adverse events during week three by treatment group.

AEs during week three	Morphine 8 mg/day ($n = 31$) number of AEs/Subjects	Morphine 16 mg/day ($n = 38$) number of AEs/Subjects	Morphine 24 mg/day ($n = 30$) number of AEs/Subjects	Morphine 32 mg/day ($n = 9$) number of AEs/Subjects	Placebo ($n = 12$) number of AEs/Subjects
Hypertension	0/0	1/1	2/2	2/2	2/2
Breathlessness	3/3	3/3	6/6	0/0	1/1
Constipation	3/3	5/5	5/4	0/0	2/1