JAMA | Original Investigation

Effect of Regular, Low-Dose, Extended-release Morphine on Chronic Breathlessness in Chronic Obstructive Pulmonary Disease
The BEAMS Randomized Clinical Trial

Magnus Ekström, MD, PhD; Diana Ferreira, MD, PhD; Sungwon Chang, PhD; Sandra Louw, BSc; Miriam J. Johnson, MD, MBChB; Danny J. Eckert, PhD; Belinda Fazekas, GDip; Katherine J. Clark, PhD; Meera R. Agar, PhD; David C. Currow, MPH, PhD; for the Australian National Palliative Care Clinical Studies Collaborative

IMPORTANCE Chronic breathlessness is common in people with chronic obstructive pulmonary disease (COPD). Regular, low-dose, extended-release morphine may relieve breathlessness, but evidence about its efficacy and dosing is needed.

OBJECTIVE To determine the effect of different doses of extended-release morphine on worst breathlessness in people with COPD after 1 week of treatment.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, double-blind, placebo-controlled randomized clinical trial including people with COPD and chronic breathlessness (defined as a modified Medical Research Council score of 3 to 4) conducted at 20 centers in Australia. People were enrolled between September 1, 2016, and November 20, 2019, and followed up through December 26, 2019.

INTERVENTIONS People were randomized 1:1:1 to 8 mg/d or 16 mg/d of oral extended-release morphine or placebo during week 1. At the start of weeks 2 and 3, people were randomized 1:1 to 8 mg/d of extended-release morphine, which was added to the prior week's dose, or placebo.

MAIN OUTCOMES AND MEASURES The primary outcome was change in the intensity of worst breathlessness on a numerical rating scale (score range, 0 [none] to 10 [being worst or most intense]) using the mean score at baseline (from days −3 to −1) to the mean score after week 1 of treatment (from days 5 to 7) in the 8 mg/d and 16 mg/d of extended-release morphine groups vs the placebo group. Secondary outcomes included change in daily step count measured using an actigraphy device from baseline (day −1) to the mean step count from week 3 (from days 19 to 21).

RESULTS Among the 160 people randomized, 156 were included in the primary analyses (median age, 72 years [IQR, 67 to 78 years]; 48% were women) and 138 (88%) completed treatment at week 1 (48 in the 8 mg/d of morphine group, 43 in the 16 mg/d of morphine group, and 47 in the placebo group). The change in the intensity of worst breathlessness at week 1 was not significantly different between the 8 mg/d of morphine group and the placebo group (mean difference, −0.3 [95% CI, −0.9 to 0.4]) or between the 16 mg/d of morphine group and the placebo group (mean difference, −0.3 [95%, CI, −1.0 to 0.4]). At week 3, the secondary outcome of change in mean daily step count was not significantly different between the 8 mg/d of morphine group and the placebo group (mean difference, −1453 [95% CI, −3310 to 405]), between the 16 mg/d of morphine group and the placebo group (mean difference, −1312 [95% CI, −3220 to 596]), between the 24 mg/d of morphine group and the placebo group (mean difference, −692 [95% CI, −2553 to 1170]), or between the 32 mg/d of morphine group and the placebo group (mean difference, −1924 [95% CI, −47 699 to 921]).

CONCLUSIONS AND RELEVANCE Among people with COPD and severe chronic breathlessness, daily low-dose, extended-release morphine did not significantly reduce the intensity of worst breathlessness after 1 week of treatment. These findings do not support the use of these doses of extended-release morphine to relieve breathlessness.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02720822

JAMA. 2022;328(20):2022-2032. doi:10.1001/jama.2022.20206

Visual Abstract

Editorial page 2014

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the Australian National Palliative Care Clinical Studies Collaborative appear in Supplement 4.

Corresponding Author: Magnus Ekström, MD, PhD, Department of Medicine, Blekinge Hospital, Bättringsvägen 1, SE-37185, Kalskrona, Sweden (pmekstrom@gmail.com).

Chronic breathlessness, defined as breathlessness at rest or with low levels of exertion that persists despite optimal treatment for the underlying conditions,[1] affects many people with chronic obstructive pulmonary disease (COPD). It often restricts activities of daily living and results in decreased physical activity and muscular and cardiovascular deconditioning, which further worsens breathlessness.[2] Chronic breathlessness is associated with anxiety and depression, reduced health-related quality of life,[3] and increased use of health care services and mortality.[4] Chronic breathlessness is often assessed using the modified Medical Research Council (MRC) scale.[5]

Opioids may reduce symptoms in people with chronic breathlessness and severe disease.[6,7] Meta-analyses of small, short-term trials suggest beneficial effects of low-dose opioids in people with chronic breathlessness,[8] including those with COPD.[9] However, a 1-week randomized clinical trial (RCT) demonstrated no statistically significant improvement in breathlessness with 20 mg/d of oral extended-release morphine vs placebo.[10] Another RCT of people with COPD and chronic breathlessness reported improved disease-specific health status after 4 weeks of treatment with low-dose, sustained-release oral morphine, and breathlessness improved in people with more severe breathlessness (modified MRC breathlessness scale score of 3 or 4).[11]

The safety of morphine for persistent breathlessness is unclear. Population-based studies of people with COPD have reported increased hospitalizations and mortality with use of morphine,[12] although these effects were not documented in people with severe, oxygen-dependent COPD.[13] Daily use of low-dose opioids (maximal dose of 20 mg/d of morphine) has not been associated with serious adverse events (hospitalization or death) in RCTs.[9-11,14]

The Breathlessness, Exertion, And Morphine Sulfate (BEAMS) trial was designed to evaluate the effect of oral extended-release morphine (8 mg/d or 16 mg/d) vs placebo on the intensity of worst breathlessness after 1 week of treatment compared with baseline. The BEAMS trial also used blinded uptitration of morphine to evaluate change in daily step count (measured using an actigraphy device) from baseline to the end of week 3.

Key Points

Question Does regular, low-dose, extended-release morphine improve the intensity of worst breathlessness in people with chronic obstructive pulmonary disease (COPD) and severe chronic breathlessness?

Findings In this randomized clinical trial including 156 people with COPD and chronic breathlessness, treatment with 8 mg/d and 16 mg/d of oral extended-release morphine for 1 week resulted in a mean difference of −0.3 and −0.3, respectively, for change in the intensity of worst breathlessness compared with placebo; neither difference was statistically significant. The scores range from 0 to 10 (a score of 10 being the worst or most intense) on the numerical rating scale that was used.

Meaning Extended-release morphine compared with placebo did not significantly reduce the intensity of worst breathlessness in people with COPD.

Methods

Trial Design and Oversight

This trial was a multicenter, placebo-controlled, phase 3, double-blind, parallel-group, dose-increment RCT of regular, low-dose, oral extended-release morphine for people with COPD and chronic breathlessness. The trial protocol was approved by the Hunter New England human research ethics committee. Each participating center obtained approval from the research governance office to recruit people to this RCT. Enrolled people provided written informed consent. The trial was conducted and monitored in accordance with Good Clinical Practice.[15] The trial protocol appears in Supplement 1 and has been published[16] and the statistical analysis plan appears in Supplement 2. This RCT is in compliance with the Consolidated Standards of Reporting Trials statement.[17] All adverse event reports and the conduct of the trial were reviewed by an independent data and safety monitoring committee.

Inclusion and Exclusion Criteria

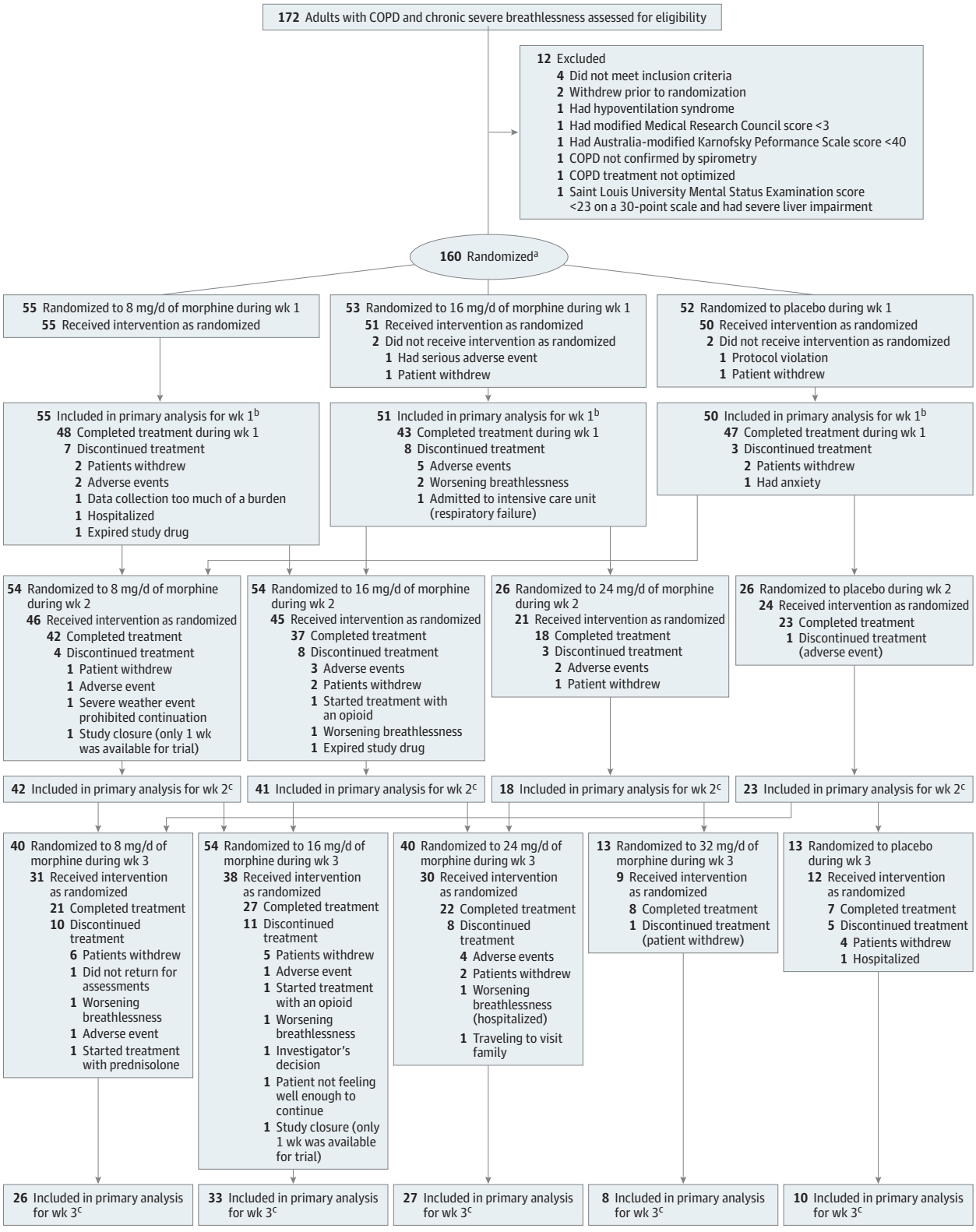
Individuals were eligible for inclusion if they met the following criteria: (1) were aged 18 years or older; (2) had a physician diagnosis of COPD[7] with postbronchodilator spirometry revealing a forced expiratory volume in the first second of expiration/forced vital capacity of less than 0.7; (3) had *severe chronic breathlessness*[1] defined as a modified MRC 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")[5] despite optimal treatment for underlying causes as confirmed by a respiratory physician; (4) had a score of 3 or greater for the intensity of worst breathlessness on a numerical rating scale (score range, 0-10) within the 24 hours before study enrollment; (5) had the ability to complete the assessments as determined by the study investigator; and (6) had been receiving stable COPD treatment during the previous week (as-needed inhaler medications were permitted; **Figure 1**).

Individuals were excluded if they (1) were currently taking opioids at any dose for breathlessness or had taken opioids during the previous week at an oral morphine equivalent dose of 8 mg/d or greater; (2) had previously experienced adverse reactions to morphine; or (3) had central hypoventilation syndrome, were pregnant, had liver or kidney failure, or had a gastrointestinal obstruction. A complete list of the inclusion and exclusion criteria appears in the trial protocol (Supplement 1).

Study Centers

The trial was coordinated by the Australian national Palliative Care Clinical Studies Collaborative and conducted at 20 oncology, palliative, or respiratory centers in Australia.[16] People were also recruited through the Lung Foundation Australia and the Primary Health Networks. All people were referred by their

Figure 1. Flow of Participants in the Breathlessness, Exertion, And Morphine Sulfate (BEAMS) Randomized Clinical Trial



COPD indicates chronic obstructive pulmonary disease.

[a] Block sizes of 6 were used to ensure even allocation at each site in a 1:1:1 for week 1; for weeks 2 and 3, randomization was 1:1 to 8 mg of morphine (which was added to the prior week's dose) or placebo.

[b] Missing data for change from baseline in the intensity of worst breathlessness were imputed using multiple imputations with 100 samples redrawn.

[c] Only people without missing data for change from baseline in the intensity of worst breathlessness were analyzed.

treating clinician to the principal investigator at each participating center.[16]

Randomization and Interventions

Participants were randomized 1:1:1 to 8 mg/d or 16 mg/d of oral extended-release morphine or placebo during week 1. All randomizations were performed at baseline using computer-generated random sample tables and permuted block sizes of 6. Each person was provided with a wrist actigraphy unit (Fitbit) and charger at the baseline visit. People were instructed to wear the actigraphy unit continuously. At the start of weeks 2 and 3, people were randomized 1:1 to 8 mg/d of extended-release morphine, which was added to the prior week's morphine dose, or placebo. Participants could then enter an optional blinded extension treatment period of 6 months (eFigure 1 in Supplement 3). The baseline step count was obtained using the wrist actigraphy unit prior to study enrollment (day −1).

The trial medications, morphine sulfate pentahydrate (Kapanol) and placebo, were provided by Mayne Pharma. They were indistinguishable in appearance and were provided by the local pharmacy in a blister pack each week. Participants were instructed to take 2 capsules of trial medication orally each morning.

Participants were also given 2 blinded tablets of laxative (docusate with sennosides for the morphine group) or placebo tablets (for those not receiving morphine) each morning. The blister packs were collected at the end of each week. Open-label laxative tablets were also available to all participants (≤2 tablets twice daily as needed).

Participants were instructed to record their level of breathlessness in a diary each evening using a validated numerical rating scale,[18] which ranged from a score of 0 (none) to 10 (being the worst or most intense). All participants received a battery-operated, handheld fan and an information sheet with standard breathlessness self-management strategies (ie, how to use the handheld fan, breathing control techniques, positions to reduce breathlessness, and suggestions to keep active). The participants were instructed to continue taking all other medications and therapies in accordance with their clinicians' recommendations throughout the study period.

Blinding

The research staff, treating clinicians, and participants were blinded to the treatment allocation. Unblinding could occur only after collection of the last data point for the final participant or in an emergency situation after consultation with the principal investigator.

Outcomes

The primary outcome was change in the intensity of worst breathlessness on a numerical rating scale (score range, 0 [none] to 10 [being the worst or most intense]) using the mean score at baseline (from days −3 to −1) to the mean score after week 1 of treatment (from days 5 to 7) in the 8 mg/d and 16 mg/d of extended-release morphine groups vs the placebo group.

The secondary outcomes included (1) change in mean daily step count measured using an actigraphy device (Fitbit) at baseline (day −1) to the mean step count at week 3 (from days 19 to 21), (2) mean change in the intensity of breathlessness and overall breathlessness distress level during the previous 24 hours, (3) Global Impression of Change in health status score,[19] (4) Hospital Anxiety and Depression Scale score,[20] (5) Australia-modified Karnofsky Performance Scale score,[21] (6) health-related quality of life measured using scores from the COPD Assessment Test, (7) the Clinical Respiratory Questionnaire Dyspnea and Mastery scores, (8) overall well-being measured using a 0- to 100-mm visual analog scale for the 5-level version of the 5-dimension EuroQol,[22] (9) symptom scores using the revised Edmonton Symptom Assessment System,[23] (10) blinded participant treatment preference, (11) end-tidal partial pressure of carbon dioxide level, (12) respiratory rate, and (13) oxygen saturation as measured by pulse oximetry.

Treatment-emergent adverse events were assessed during a mid-week telephone call and at the review at the end of each week[16] using version 4 of the National Cancer Institute Common Terminology Criteria for Adverse Events.[24] A treatment-emergent adverse event was any event that occurred or worsened after baseline. Treatment-emergent adverse events with a grade of 3 or greater using the National Cancer Institute Common Terminology Criteria for Adverse Events, or those otherwise reported as serious adverse events as part of the trial's pharmacovigilance reporting, were categorized as severe treatment-emergent adverse events. Outcomes were evaluated after 1 week for the primary outcome and after 3 weeks for the secondary outcomes.

Sample Size

We estimated that a sample of 135 people would provide 80% power to detect a minimal clinically important difference of 1.1 point for the primary outcome using a numerical rating scale with a score range from 0 (none) to 10 (being the worst or most intense)[25] and with an SD range of 2.0 to 2.5 each day during week 1. Sample size calculations were based on a recent RCT.[10] The type I error rate was prespecified as 2.5% (2-sided α level of .025) for the primary analysis and comprised 2 comparisons: 8 mg of morphine vs placebo and 16 mg of morphine vs placebo. Using a mixed-linear regression model and variance-covariance matrix based on the mean responses from the recent RCT,[10] 45 participants per group were required to remain in the trial after week 1.

Statistical Methods

The categorical variables are expressed as number (percentage) and the continuous variables are expressed as median (IQR). The analyses were conducted according to randomization group. For both the efficacy analyses and the safety analyses, the analysis set was all randomized participants who received at least 1 dose of study medication.

The treatment effects for the intensity of worst breathlessness and the step count outcomes were analyzed using random-effects mixed-linear regression models, with the change from baseline as the dependent variable; treatment group, day, and treatment group × day as interaction factors; and adjustment for the baseline values of age, sex, modified MRC breathlessness scale score, Australia-modified Karnofsky Performance Scale score, end-tidal partial pressure of carbon dioxide,

oxygen saturation as measured by pulse oximetry, and Charlson Comorbidity Index. An unstructured variance-covariance structure was used for the primary outcome of change in the intensity of worst breathlessness.

Compound symmetry and Toeplitz variance-covariance structures were used for the secondary outcome of step count. For the other secondary outcomes, the treatment effects were analyzed using analysis of covariance with change from baseline to end of the week as the dependent variable, treatment group as a factor, and adjustment for the baseline values of age, sex, modified MRC breathlessness scale score, Australia-modified Karnofsky Performance Scale score, end-tidal partial pressure of carbon dioxide, oxygen saturation as measured by pulse oximetry, and Charlson Comorbidity Index. The primary analysis was conducted without and with imputation for missing outcome data using multiple imputations with 100 samples redrawn. The secondary analyses were conducted using observed data without imputation. After week 1, treatment with 8 mg/d and 16 mg/d of extended-release morphine was compared with placebo for the primary analysis of change in the intensity of worst breathlessness, and after week 3, each allocated morphine treatment group (8 mg/d, 16 mg/d, 24 mg/d, and 32 mg/d) was compared with placebo.

All between-group analyses were reported with 95% CIs. Statistical significance at the end of week 1 was defined as a 2-sided *P* value of <.025 for the primary outcome analysis of change in the intensity of worst breathlessness after treatment with morphine (8 mg/d or 16 mg/d) vs placebo. The secondary outcome of step count was assessed at the end of week 3 and used a 2-sided significance level of .0125 after treatment with morphine (8 mg/d, 16 mg/d, 24 mg/d, or 32 mg/d) vs placebo. A hierarchical testing procedure was used whereby if the primary outcome was not significant, the secondary outcome of step count would be tested but only reported as exploratory or hypothesis-generating. All other statistical tests were 2-sided at the 5% significance level. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc).

Results

People were enrolled between September 1, 2016, and November 20, 2019, and followed up through December 26, 2019, at 20 centers. Of the 160 people who were randomized, 55 were randomized to 8 mg/d of morphine, 53 to 16 mg/d of morphine, and 52 to placebo (Figure 1). During week 1, there were 2 people in 16 mg/d of morphine group and 2 people in the placebo group who did not take any study drug and these people were excluded from the primary analyses. Of the 156 people included in the primary analyses (median age, 72 years [IQR, 67-78 years]; 48% were women), 121 (78%) had a score of 3 on the modified MRC breathlessness scale and 35 (22%) had a score of 4.

The baseline characteristics were similar among the treatment groups (**Table 1**). At baseline, the mean step counts were similar among the groups: 2526 (SD, 2139) for the 8 mg/d of morphine group, 2214 (SD, 1801) for the 16 mg/d of morphine group, and 2242 (SD, 1708) for the placebo group (**Table 2**). A total of 21 people completed 3 weeks of treatment in the 8 mg/d of morphine group, 27 people in the 16 mg/d of morphine group, 22 people in the 24 mg/d of morphine group, 8 people in the 32 mg/d of morphine group, and 7 people in the placebo group (Figure 1).

Primary Outcome

After 1 week of treatment, the primary outcome of change in the intensity of worst breathlessness was not significantly different for the 8 mg/d of morphine group vs placebo (mean difference, −0.3 [95% CI, −0.9 to 0.4]) or for 16 mg/d of morphine group vs placebo (mean difference, −0.3 [95% CI, −1.0 to 0.4]) (Table 2 and **Figure 2**). There was no significant treatment effect when accounting for missing data using multiple imputation for the 8 mg/d of morphine group vs the placebo group (mean difference, −0.20 [95% CI, −0.86 to 0.46]) or for the 16 mg/d of morphine group vs the placebo group (mean difference, −0.30 [95% CI, −0.98 to 0.38]).

Overall in the primary outcome analysis including 156 people, data were missing for 10 (6%). Of the missing data for the 10 people, 1 was in the 8 mg/d of morphine group, 6 were in the 16 mg/d of morphine group, and 3 were in the placebo group. The primary outcome of change in the intensity of worst breathlessness was not significantly different among people with a modified MRC breathlessness scale score of 3 or 4 (eFigure 2 in Supplement 3) or when analyzed per protocol (mean difference, −0.20 [95% CI, −0.86 to 0.46] for the 8 mg/d of morphine group vs the placebo group; mean difference, −0.30 [95% CI, −0.98 to 0.38] for the 16 mg/d of morphine group vs the placebo group).

Secondary Outcomes

After 3 weeks of treatment, there were no significant differences for the secondary outcome of change in mean daily step count for the 8 mg/d of morphine group vs the placebo group (mean difference, −1453 [95% CI, −3310 to 405]), for the 16 mg/d of morphine group vs the placebo group (mean difference, −1312 [95% CI, −3220 to 596]), for the 24 mg/d of morphine group vs the placebo group (mean difference, −692 [95% CI, −2553 to 1170]), or for the 32 mg/d of morphine group vs the placebo group (mean difference, −1924 [95% CI, −47 699 to 921]) (Figure 2). None of the secondary outcomes were significantly different between the treatment groups after week 1 (Table 2 and eTables 2-3 in Supplement 3), including for change in mean daily step count (eFigure 3 in Supplement 3) and change in the mean intensity of breathlessness and overall breathlessness distress level (eFigure 4 in Supplement 3).

Based on capsule count at the end of the study periods, adherence to the allocated treatment was very high and similar among the groups. Mean adherence was 97% to 100% during week 1 (eTable 4 in Supplement 3), 95% to 100% during week 2 (eTable 5 in Supplement 3), and 93% to 100% during week 3 (eTable 6 in Supplement 3).

Adverse Events

Treatment-emergent adverse events during week 1 occurred in 35 of 55 people (64%) in the 8 mg/d of morphine group, 40 of 51 people (78%) in the 16 mg/d of morphine group, and 24

Table 1. Baseline Characteristics of the Participants

	8 mg/d of morphine (n = 55)[a]	16 mg/d of morphine (n = 51)[a]	Placebo (n = 50)[a]
Age, median (IQR), y	73 (67-78)	73 (67-78)	72 (66-76)
Sex			
Male	28 (51)	25 (49)	28 (56)
Female	27 (49)	26 (51)	22 (44)
Body mass index, median (IQR)[b]	26.1 (22.4-31.2)	27.0 (23.0-31.6)	25.9 (21.7-30.5)
Smoking status			
Former	43 (78)	43 (84)	38 (76)
Current	10 (18)	6 (12)	12 (24)
Never	2 (4)	2 (4)	0
Living arrangement			
Private residence	53 (96)	51 (100)	47 (94)
Residential care facility	1 (2)	0	3 (6)
Inpatient palliative care unit	1 (2)	0	0
Had a caregiver, No./total (%)	33/49 (67)	38/46 (83)	32/48 (67)
Modified Medical Research Council breathlessness scale score[c]			
3[d]	49 (89)	38 (75)	34 (68)
4	6 (11)	13 (25)	16 (32)
Charlson Comorbidity Index[e]			
0	22 (40)	19 (37)	23 (46)
1-2	23 (42)	23 (45)	17 (34)
≥3	10 (18)	9 (18)	10 (20)
Other causes of breathlessness			
Had ≥1 other cause of breathlessness	28 (51)	24 (47)	21 (42)
Heart failure	12 (22)	12 (24)	5 (10)
Asthma	6 (11)	5 (10)	7 (14)
Restrictive lung disease	4 (7)	2 (4)	3 (6)
Thromboembolic cause	3 (6)	2 (4)	2 (4)
Bronchiectasis	2 (4)	1 (2)	1 (2)
Lung cancer or metastasis	1 (2)	1 (2)	2 (4)
Lung infection or inflammation	1 (2)	0	2 (4)
Other[f]	10 (18)	8 (16)	12 (24)
Supplemental oxygen therapy			
No	28 (51)	29 (56)[g]	33 (66)
Yes			
Continuous use [usual flow rate, median {IQR}, L/min]	16 (29) [2.0 {2.0-2.0}]	10 (20)[g] [2.0 {1.5-2.5}]	9 (18) [2.0 {1.5-2.0}]
Only on exertion	3 (5)	7 (14)[g]	3 (6)
Only when needed	8 (15)	4 (8)[g]	5 (10)

[a] Data are expressed as No. (%) unless otherwise indicated. Week 3 data (morphine dose groups of 8 mg/d, 16 mg/d, 24 mg/d, and 32 mg/d vs placebo) appear in eTable 1 in Supplement 3.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Ordinal scale with scores that range from 0 to 4; the worst score is 4.

[d] Corresponds to responses such as "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."

[e] Scores range from 0 to 37; higher scores indicate worse comorbidity. Based on the presence of 19 comorbidities.

[f] Anemia, anxiety, arrhythmia, muscular and cardiovascular deconditioning, ischemic heart disease, being overweight or obese, pulmonary fibrosis, pulmonary hypertension, and valvular disease.

[g] The denominator is 50 people.

of 50 people (48%) in the placebo group (eTables 7-8 in Supplement 3). The treatment-emergent adverse events were common morphine-related adverse events and included constipation, fatigue, dizziness, nausea, and vomiting. However, these treatment-emergent adverse events did not appear to be associated with study drug adherence (eTables 4-6 in Supplement 3). Treatment-emergent adverse events during weeks 2 and 3 appear in eTables 9-10 in Supplement 3.

During week 1, the number of people who discontinued treatment due to adverse events was 2 in the 8 mg/d of morphine group and 5 in the 16 mg/d of morphine group, and 0 in the placebo group (Figure 1). During week 2, study discontinuation due to adverse events occurred in 1 person in the 8 mg/d of morphine group, in 3 people in the 16 mg/d of morphine group, in 2 people in the 24 mg/d of morphine group, and in 1 person in the placebo group (Figure 1). During week 3, study

Table 2. Primary Outcome, Secondary Outcomes, and Other Outcome Measures at Week 1

	Outcome score, mean (SD)[a]									Adjusted between-group difference, mean (95% CI)[b]	
	8 mg/d of morphine			16 mg/d of morphine			Placebo				
	At baseline (−3 to −1 d)[c]	At wk 1 (5 to 7 d)[d]	Unadjusted within-group change	At baseline (−3 to −1 d)[c]	At wk 1 (5 to 7 d)[d]	Unadjusted within-group change	At baseline (−3 to −1 d)[c]	At wk 1 (5 to 7 d)[d]	Unadjusted within-group change	8 mg/d of morphine vs placebo	16 mg/d of morphine vs placebo
Primary outcome											
Intensity of worst breathlessness[e]	5.9 (1.5)	5.1 (2.1)	−0.8 (1.7)	6.5 (1.7)	5.6 (2.1)	−1.0 (1.7)	6.2 (1.4)	5.4 (2.2)	−0.7 (1.7)	−0.3 (−0.9 to 0.4)	−0.3 (−1.0 to 0.4)
Secondary outcomes											
Daily step count[f]	2526 (2139)	2392 (1867)	84 (1003)	2214 (1801)	1938 (1388)	−399 (956)	2242 (1708)	2430 (2246)	99 (1329)	39 (−501 to 579)	−388 (−1053 to 277)
Symptoms											
Intensity of breathlessness[e]	4.6 (1.5)	4.0 (1.9)	−0.6 (1.4)	5.1 (1.7)	4.6 (2.3)	−0.5 (1.7)	5.0 (1.6)	4.4 (2.2)	−0.6 (1.5)	−0.1 (−0.7 to 0.5)	0 (−0.6 to 0.7)
Overall breathlessness distress level[e]	4.1 (2.4)	3.0 (2.5)	−1.0 (2.2)	4.8 (2.4)	3.5 (2.5)	−1.3 (2.3)	4.0 (2.5)	3.2 (2.7)	−0.7 (1.5)	−0.4 (−1.1 to 0.4)	−0.4 (−1.2 to 0.4)
Hospital Anxiety and Depression Scale[g]											
Anxiety	6.8 (3.9)	5.5 (3.5)	−1.2 (3.0)	6.4 (3.7)	5.6 (3.2)	−0.5 (2.8)	5.7 (3.7)	5.6 (3.9)	0.1 (3.2)	−0.4 (−1.5 to 0.8)	0.1 (−1.1 to 1.2)
Depression	6.3 (3.2)	5.3 (2.8)	−0.7 (1.7)	7.0 (4.0)	6.3 (3.9)	−0.8 (2.6)	6.2 (3.4)	6.2 (3.2)	0.3 (2.2)	−0.8 (−1.7 to 0.1)	−0.8 (−1.7 to 0.1)
Function											
Australia-modified Karnofsky Performance Scale[h]	66.0 (8.9)	66.7 (9.4)	−0 (1.8)	64.7 (8.6)	65.0 (8.9)	0.2 (5.8)	64.6 (8.9)	64.2 (8.7)	−0.4 (4.1)	1.4 (−0.9 to 3.7)	0.9 (−1.4 to 3.3)
Health-related quality of life											
COPD Assessment Test[i]	21.5 (6.5)	18.7 (6.1)	−3.1 (5.6)	22.9 (5.5)	19.7 (6.1)	−3.2 (4.7)	23.8 (6.3)	20.9 (5.4)	−2.9 (4.6)	−0.8 (−2.7 to 1.0)	−0.6 (−2.5 to 1.2)
Clinical Respiratory Questionnaire[j]											
Dyspnea	3.5 (0.9)	3.8 (1.1)	0.3 (1.1)	3.2 (1.4)	3.7 (1.3)	0.4 (1.4)	3.4 (1.3)	3.6 (1.3)	0.2 (1.3)	0.1 (−0.3 to 0.5)	0.1 (−0.3 to 0.6)
Mastery	4.0 (1.0)	4.2 (0.7)	0.1 (0.8)	4.2 (0.9)	4.2 (0.7)	0 (0.9)	3.9 (0.8)	4.0 (0.8)	0.1 (1.1)	0.2 (−0.1 to 0.5)	0.1 (−0.2 to 0.4)
5-level version of the 5-dimension EuroQol[k]	63.0 (18.0)	64.5 (17.7)	2.3 (18.8)	57.9 (19.9)	61.2 (20.8)	3.5 (18.8)	59.1 (20.0)	64.1 (18.7)	3.8 (18.5)	−0.7 (−7.3 to 6.0)	−1.8 (−8.7 to 5.1)
Physiological parameters											
End-tidal partial pressure of carbon dioxide, mm Hg	27.2 (8.2)	27.7 (8.0)	0.6 (9.8)	28.0 (8.3)	28.4 (7.4)	0.1 (6.6)	27.6 (11.6)	26.4 (7.9)	−1.6 (12.1)	2.0 (−1.0 to 5.0)	2.0 (−1.2 to 5.1)
Oxygen saturation as measured by pulse oximetry, %[l]	92.7 (3.8)	91.5 (3.5)	−1.3 (3.3)	90.9 (12.3)	90.9 (2.8)	0.1 (12.7)	93.2 (3.7)	90.9 (13.8)	−2.2 (13.5)	1.5 (−2.0 to 4.9)	0.7 (−2.9 to 4.2)
Respiratory rate, min^{-1}	22.3 (10.8)	21.5 (10.8)	−1.1 (13.3)	19.8 (4.9)	19.6 (4.5)	−0.2 (4.3)	21.2 (4.5)	21.4 (4.3)	0.2 (4.2)	−0.7 (−3.6 to 2.1)	−1.6 (−4.5 to 1.4)

(continued)

Table 2. Primary Outcome, Secondary Outcomes, and Other Outcome Measures at Week 1 (continued)

	Outcome score, mean (SD)[a]									Adjusted between-group difference, mean (95% CI)[b]	
	8 mg/d of morphine			16 mg/d of morphine			Placebo				
	At baseline (−3 to −1 d)[c]	At wk 1 (5 to 7 d)[d]	Unadjusted within-group change	At baseline (−3 to −1 d)[c]	At wk 1 (5 to 7 d)[d]	Unadjusted within-group change	At baseline (−3 to −1 d)[c]	At wk 1 (5 to 7 d)[d]	Unadjusted within-group change	8 mg/d of morphine vs placebo	16 mg/d of morphine vs placebo
Other outcomes											
Revised version of the Edmonton Symptom Assessment Scale[e]											
Pain	1.3 (2.0)	1.3 (2.2)	−0 (1.8)	1.8 (2.4)	1.2 (2.0)	−0.3 (2.1)	2.0 (2.4)	1.4 (1.9)	−0.5 (1.8)	0.2 (−0.5 to 0.8)	0 (−0.7 to 0.7)
Tiredness	2.7 (2.0)	2.3 (2.2)	−0.3 (2.5)	3.5 (2.6)	3.5 (2.7)	0.2 (2.6)	3.7 (2.7)	3.1 (2.6)	−0.5 (2.8)	−0.4 (−1.3 to 0.6)	0.5 (−0.5 to 1.4)
Nausea	0.4 (1.4)	0.3 (0.7)	−0.2 (1.6)	0.3 (0.9)	0.4 (1.6)	0.2 (1.6)	0.5 (1.7)	0.3 (1.0)	−0.3 (1.6)	−0.1 (−0.6 to 0.4)	0.2 (−0.3 to 0.6)
Depression	1.1 (1.8)	0.7 (1.2)	−0.3 (1.6)	1.6 (2.4)	1.3 (2.5)	−0.2 (2.7)	1.3 (2.5)	1.3 (2.4)	0 (2.7)	−0.4 (−1.2 to 0.4)	0 (−0.8 to 0.8)
Anxiety	1.2 (2.0)	1.0 (1.6)	−0.2 (1.4)	1.6 (2.3)	1.5 (2.5)	0 (2.3)	1.6 (2.6)	1.4 (2.3)	−0 (2.8)	−0.3 (−1.0 to 0.5)	0 (−0.7 to 0.8)
Drowsiness	1.4 (1.9)	1.6 (2.1)	0.4 (1.8)	2.3 (2.6)	3.2 (2.7)	1.0 (2.7)	2.7 (2.6)	1.9 (2.3)	−0.8 (2.5)	0.5 (−0.4 to 1.3)	1.6 (0.7 to 2.4)
Lack of appetite	1.7 (2.4)	1.6 (2.4)	−0 (2.1)	1.4 (2.6)	1.5 (2.7)	0.4 (2.4)	2.1 (3.0)	1.4 (2.3)	−0.8 (2.6)	0.2 (−0.6 to 1.0)	0.5 (−0.4 to 1.3)
Breathlessness	3.9 (2.8)	3.3 (2.5)	−0.6 (2.4)	4.3 (3.3)	4.0 (3.1)	−0.2 (2.9)	5.2 (2.9)	4.4 (2.6)	−0.2 (2.9)	−0.5 (−1.4 to 0.5)	0.1 (−0.9 to 1.1)
Well-being	3.2 (1.9)	3.1 (2.2)	0 (2.0)	4.1 (2.4)	3.8 (2.4)	−0.4 (2.0)	3.8 (2.3)	3.7 (2.1)	−0 (2.9)	−0.2 (−1.0 to 0.6)	−0.2 (−1.0 to 0.7)

Abbreviation: COPD, chronic obstructive pulmonary disease.

[a] The majority of outcomes are scores from a scale or questionnaire, but some of the rows under "symptoms" and "physiological parameters" are not. Additional categorical outcomes appear in Supplement 3 (eTable 2 has outcomes after week 1 of treatment and eTable 3 has outcomes after week 3).

[b] Between-group difference in the change from baseline after 1 week with morphine vs placebo. A negative value is interpreted as a decrease in the outcome with morphine vs placebo. For the breathlessness and step count outcomes, the treatment effects were analyzed using random-effects mixed-linear regression models with the change from baseline as the dependent variable; treatment group, day, and treatment group × day as interaction factors; and adjustment for the baseline values of age, sex, modified Medical Research Council breathlessness scale score, Australia-modified Karnofsky Performance Scale score, end-tidal partial pressure of carbon dioxide, oxygen saturation as measured by pulse oximetry, and Charlson Comorbidity Index. An unstructured variance-covariance structure was used for the numerical rating scale used to assess the primary outcome of intensity of worst breathlessness. A compound symmetry variance-covariance structure was used to assess the secondary outcome of daily step count. For the other secondary outcomes, treatment effects were analyzed using analysis of covariance with change from baseline to end of the week as the dependent variable, treatment group as a factor, and adjustment for the baseline values of age, sex, modified Medical Research Council breathlessness scale score, Australia-modified Karnofsky Performance Scale score, end-tidal partial pressure of carbon dioxide, oxygen saturation as measured by pulse oximetry, and Charlson Comorbidity Index.

[c] Mean of 3 days before the day of first study drug administration. However, for step count, baseline was the full 24 hours (midnight to midnight) on the day before randomization.

[d] Mean of the last 3 days of the week to try to ensure measurement while receiving the allocated treatment at steady state.

[e] Measured on a numerical rating scale with scores between 0 (none) and 10 (worst or most intense).

[f] Measured using an actigraphy device (Fitbit) for 24 hours at baseline and the mean of three 24-hour days at the end of weeks 1 and 3.

[g] Scores range from 0 (best) to 21 (worst).

[h] Measure of overall functional status assigned by staff based on observations of a participant's ability to perform common tasks relating to activity, work, and self-care. Scored between 100 (normal) and 10 (comatose or barely rousable).

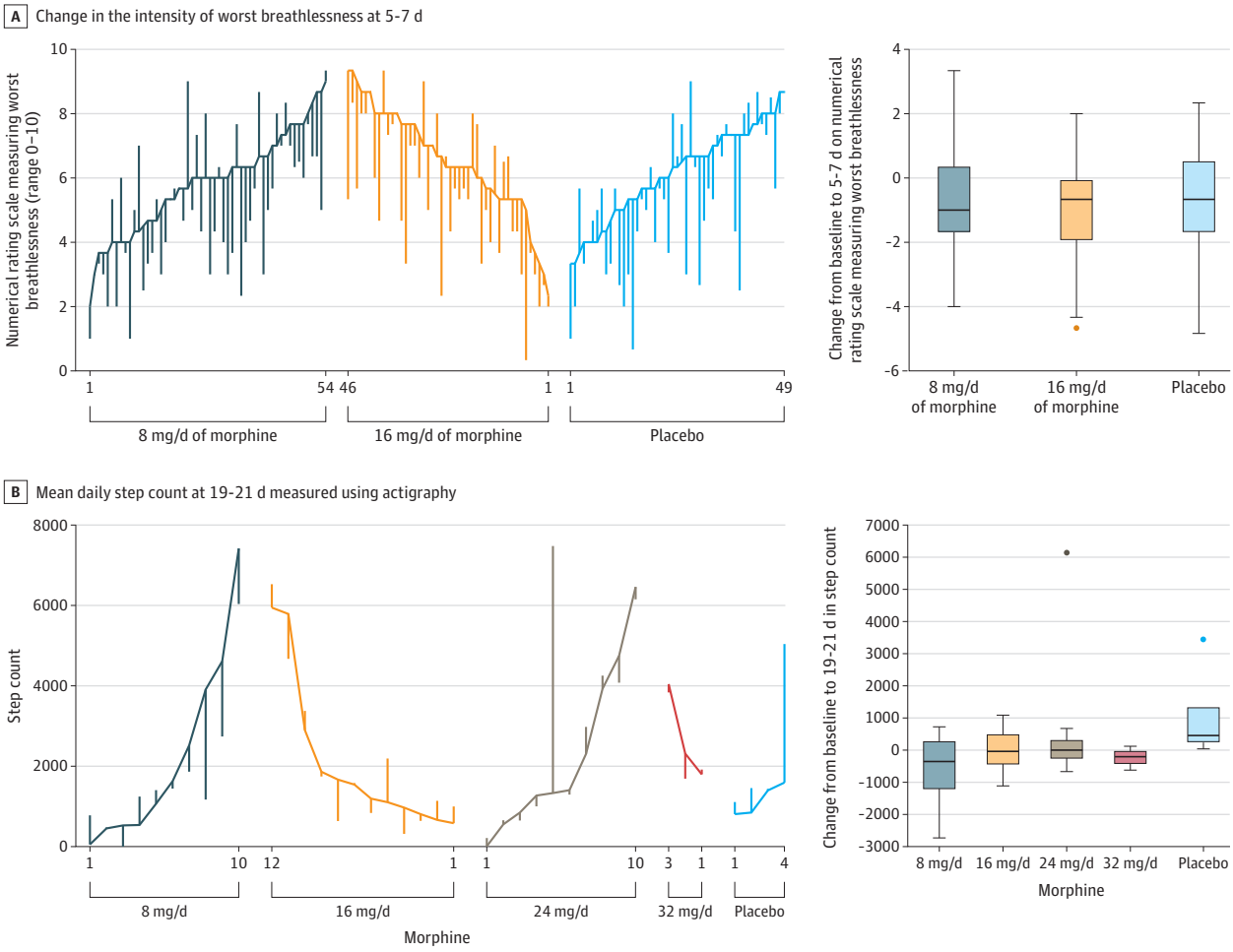
[i] Measure of health-related quality of life. Scores range from 0 (best) to 40 (worst).

[j] Measure of health-related quality of life. Scores range from 1 (worst) to 7 (best).

[k] Measure of the self-rated perceived overall well-being on a 100-mm visual analog scale. Scores range from 0 (worst) to 100 (best).

[l] Measured after optimization of treatment for COPD and, for some participants, included use of supplemental oxygen.

Figure 2. Change in the Intensity of Worst Breathlessness and Mean Daily Step Count



The parallel line plots display the individual results at baseline and follow-up (change in the intensity of worst breathlessness at days 5-7 and change in mean step count at days 19-21) for each person. The baseline results are plotted with the follow-up result connected by a vertical line. People are ordered from left to right by increasing baseline values for 8 mg/d of morphine and placebo and 24 mg/d of morphine and decreasing baseline values for 16 mg/d of morphine and 32 mg/d of morphine. The boxes represent the IQRs for the change from baseline to follow-up, with the horizontal black line in the middle representing the median. The whiskers represent the smallest and largest values within 1.5 × the IQR of the first quartile and third quartile, respectively. The dots represent points outside the range.

discontinuation due to adverse events occurred in 1 person in the 8 mg/d of morphine group, in 1 person in 16 mg/d of morphine group, in 4 people in the 24 mg/d of morphine group, in 0 people in the 32 mg/d of morphine group, and in 0 people in the placebo group.

Throughout the trial, serious treatment-emergent adverse events (which included hospitalizations and deaths) occurred in 46 of 139 people (33%; 85 episodes) who received any dose of morphine compared with 2 of 17 people (12%; 2 episodes) who received only placebo (**Table 3**). Serious treatment-emergent adverse events included increased breathlessness, infections, morphine-related adverse events, and 2 events that met the criteria[24] for respiratory failure (both in the morphine group) of the National Cancer Institute Common Terminology Criteria for Adverse Events.

Discussion

In this RCT of people with COPD and severe chronic breathlessness, daily treatment with extended-release morphine did not significantly improve the primary outcome of change in the intensity of worst breathlessness after 1 week of treatment. There was also no significant improvement in the secondary outcome of mean daily step count using an actigraphy device or in any of the other secondary outcomes, including symptoms, function, health-related quality of life, and physiological parameters. The lack of efficacy was consistent across severities of breathlessness (modified MRC breathlessness scale score of 3 or 4).

This RCT tested the efficacy and adverse event profile of several different uptitrated doses of extended-release

Table 3. Serious Treatment-Emergent Adverse Events (TEAEs), Hospitalizations, and Deaths

	No. (%) of participants				
	Morphine[a]				
	8 mg/d (n = 43)	16 mg/d (n = 54)	24 mg/d (n = 33)	32 mg/d (n = 9)	Placebo (n = 17)
≥1 Serious TEAE[b]	8 (19)	10 (19)	2 (6)	0	1 (6)
Hospitalizations	7 (16)	8 (15)	3 (9)	0	1 (6)
Deaths	0	1 (2)	0	0	0

[a] Participants are grouped by the highest dose of morphine they received during the trial.

[b] Included increased breathlessness, infections, morphine-related adverse events, and 2 events that met the criteria[24] for respiratory failure (both in the morphine group) of the National Cancer Institute Common Terminology Criteria for Adverse Events.

morphine across clinically relevant doses (8 mg/d, 16 mg/d, 24 mg/d, and 32 mg/d) over 3 weeks in people with COPD and severe chronic breathlessness. To our knowledge, this study is the first to measure physical function using an actigraphy device concurrently with blinded uptitration of morphine in an adequately powered trial. These doses of extended-release morphine were not associated with a decreased total step count compared with placebo. The unchanged total step count does not support the hypothesis that the lack of efficacy on breathlessness was due to people increasing their physical activity (thereby masking a true symptom improvement).[10,26]

The study findings may not be applicable to people with very advanced COPD and breathlessness who are in palliative care or near the end of life, at which time treatment with opioids may be useful to provide relief of severe dyspnea.[4,27] Further research is needed to determine if specific groups of people with COPD are more likely to experience a reduction in breathlessness with morphine, if some may benefit from higher doses of morphine, and to clarify the role of short-acting opioids for severe episodes of breathlessness.

Strengths of this study include its multicenter, double-blind, parallel-group randomized design and blinded uptitration during each stage of the trial vs placebo. Blinded administration of laxative (or placebo) improved blinding; participants were not allowed to take as-needed morphine during the trial, and clinically relevant efficacy and safety outcomes were assessed using validated instruments.[28]

Limitations

This study has several limitations. First, the number of participants in each group decreased over the 3-week period, and only 42% completed treatment at week 3. However, the trial was adequately powered for the primary outcome and recruited the target number of people.

Second, breathlessness was measured in daily life and not during standardized exercise testing. Third, extended-release morphine can be administered every 12 hours to 24 hours so it is possible that the 24-hour dosing interval used in this study may have provided a suboptimal dose.

Conclusions

Among people with COPD and severe chronic breathlessness, daily low-dose, extended-release morphine did not significantly reduce the intensity of worst breathlessness after 1 week of treatment. These findings do not support the use of these doses of extended-release morphine to relieve breathlessness.

ARTICLE INFORMATION

Accepted for Publication: October 12, 2022.

Author Affiliations: Faculty of Medicine, Department of Clinical Sciences, Respiratory Medicine, Allergology, and Palliative Medicine, Lund University, Lund, Sweden (Ekström); Faculty of Health Improving Palliative, Aged, and Chronic Care Through Clinical Research and Translation, University of Technology Sydney, Ultimo, Australia (Ekström, Chang, Fazekas, Agar); Faculty of Science, Medicine, and Health, University of Wollongong, Wollongong, Australia (Ferreira, Currow); McCloud Consulting Group, Belrose, Australia (Louw); Wolfson Palliative Care Research Centre, Hull York Medical School, University of Hull, Hull, England (Johnson); Adelaide Institute for Sleep Health, Flinders University, Adelaide, Australia (Eckert); Palliative Care Network, Northern Sydney Local Health District, Sydney, Australia (Clark); Northern Clinical School, University of Sydney, Sydney, Australia (Clark); Palliative and Supportive Services, Flinders University, Adelaide, Australia (Currow).

Author Contributions: Dr Currow had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Ekström, Ferreira, Johnson, Eckert, Fazekas, Clark, Agar, Currow.
Acquisition, analysis, or interpretation of data: Ekström, Ferreira, Chang, Louw, Johnson, Eckert, Fazekas, Agar, Currow.
Drafting of the manuscript: Ekström, Agar, Currow.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Louw, Currow.
Obtained funding: Johnson, Currow.
Administrative, technical, or material support: Ekström, Ferreira, Eckert, Fazekas, Agar, Currow.
Supervision: Fazekas.

Conflict of Interest Disclosures: Dr Ekström reported receiving an unrestricted grant from the Swedish Research Council. Ms Louw reported being employed by McCloud Consulting Group and receiving consulting fees for her work on this study and receiving personal fees from the Palliative Care Clinical Studies Collaborative. Dr Johnson reported receiving consulting fees from Mayne Pharma for serving as a clinical advisor. Dr Eckert reported receiving a Collaborative Research Centre Consortium grant among his institution, the Australian government, and Oventus Medical; receiving grants from the National Health and Medical Research Council (NHMRC) of Australia, Takeda, Bayer, Invicta Medical, and Apnimed; being supported by a leadership fellowship sponsored by the NHMRC of Australia; serving as a consultant to Bayer, Apnimed, and Takeda; receiving personal fees from Eisai; and serving on advisory boards for Eisai, Invicta Medical, and Apnimed. Dr Agar reported receiving payment from AstraZeneca to facilitate a workshop on the multidisciplinary care of older people with lung cancer. Dr Currow reported receiving an unrestricted grant from Mundipharma; being an unpaid member of an advisory board for Helsinn Pharmaceuticals; and being a consultant for and receiving intellectual property payments from Mayne Pharma. No other disclosures were reported.

Funding/Support: This study was funded by grant APP1065571 from the National Health and Medical Research Council of Australia and sponsored by Flinders University, Adelaide, Australia.

Role of the Funder/Sponsor: The National Health and Medical Research Council of Australia and

Flinders University had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The members of the Australian National Palliative Care Clinical Studies Collaborative appear in Supplement 4.

Data Sharing Statement: See Supplement 5.

Additional Contributions: We thank all participants who made this research possible at a very difficult time of their life, and to the families and friends who supported them. Thanks also go to the staff at each site for their enduring efforts in working with participants to complete the study.

REFERENCES

1. Johnson MJ, Yorke J, Hansen-Flaschen J, et al. Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. *Eur Respir J*. 2017;49(5):1602277. doi:10.1183/13993003.02277-2016

2. O'Donnell CR, Schwartzstein RM, Lansing RW, Guilfoyle T, Elkin D, Banzett RB. Dyspnea affective response: comparing COPD patients with healthy volunteers and laboratory model with activities of daily living. *BMC Pulm Med*. 2013;13(1):27. doi:10.1186/1471-2466-13-27

3. Currow DC, Dal Grande E, Ferreira D, Johnson MJ, McCaffrey N, Ekström M. Chronic breathlessness associated with poorer physical and mental health–related quality of life (SF-12) across all adult age groups. *Thorax*. 2017;72(12):1151-1153. doi:10.1136/thoraxjnl-2016-209908

4. Ekström MP, Abernethy AP, Currow DC. The management of chronic breathlessness in patients with advanced and terminal illness. *BMJ*. 2015;350:g7617. doi:10.1136/bmj.g7617

5. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*. 1999;54(7):581-586. doi:10.1136/thx.54.7.581

6. Hui D, Bohlke K, Bao T, et al. Management of dyspnea in advanced cancer: ASCO guideline. *J Clin Oncol*. 2021;39(12):1389-1411. doi:10.1200/JCO.20.03465

7. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of COPD. Accessed February 5, 2022. https://goldcopd.org/

8. Ekström M, Bajwah S, Bland JM, Currow DC, Hussain J, Johnson MJ. One evidence base; three stories: do opioids relieve chronic breathlessness? *Thorax*. 2018;73(1):88-90. doi:10.1136/thoraxjnl-2016-209868

9. Ekström M, Nilsson F, Abernethy AA, Currow DC. Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease: a systematic review. *Ann Am Thorac Soc*. 2015;12(7):1079-1092. doi:10.1513/AnnalsATS.201501-034OC

10. Currow D, Louw S, McCloud P, et al; Australian National Palliative Care Clinical Studies Collaborative (PaCCSC). Regular, sustained-release morphine for chronic breathlessness: a multicentre, double-blind, randomised, placebo-controlled trial. *Thorax*. 2020;75(1):50-56. doi:10.1136/thoraxjnl-2019-213681

11. Verberkt CA, van den Beuken-van Everdingen MHJ, Schols JMGA, Hameleers N, Wouters EFM, Janssen DJA. Effect of sustained-release morphine for refractory breathlessness in chronic obstructive pulmonary disease on health status: a randomized clinical trial. *JAMA Intern Med*. 2020;180(10):1306-1314. doi:10.1001/jamainternmed.2020.3134

12. Vozoris NT, Wang X, Fischer HD, et al. Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J*. 2016;48(3):683-693. doi:10.1183/13993003.01967-2015

13. Ekström MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ*. 2014;348:g445. doi:10.1136/bmj.g445

14. Verberkt CA, van den Beuken-van Everdingen MHJ, Schols JMGA, et al. Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. *Eur Respir J*. 2017;50(5):1701153. doi:10.1183/13993003.01153-2017

15. European Medicines Agency. *ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice*. European Medicines Agency; 2002.

16. Currow D, Watts GJ, Johnson M, et al; Australian national Palliative Care Clinical Studies Collaborative (PaCCSC). A pragmatic, phase III, multisite, double-blind, placebo-controlled, parallel-arm, dose increment randomised trial of regular, low-dose extended-release morphine for chronic breathlessness: Breathlessness, Exertion And Morphine Sulfate (BEAMS) study protocol. *BMJ Open*. 2017;7(7):e018100. doi:10.1136/bmjopen-2017-018100

17. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med*. 2010;152(11):726-732. doi:10.7326/0003-4819-152-11-201006010-00232

18. Wilcock A, Crosby V, Clarke D, Tattersfield A. Repeatability of breathlessness measurements in cancer patients. *Thorax*. 1999;54(4):375. doi:10.1136/thx.54.4.374b

19. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole MR. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94(2):149-158. doi:10.1016/S0304-3959(01)00349-9

20. Nowak C, Sievi NA, Clarenbach CF, et al. Accuracy of the Hospital Anxiety and Depression Scale for identifying depression in chronic obstructive pulmonary disease patients. *Pulm Med*. 2014;2014:973858. doi:10.1155/2014/973858

21. Abernethy AP, Shelby-James T, Fazekas BS, Woods D, Currow DC. The Australia-modified Karnofsky Performance Status (AKPS) scale: a revised scale for contemporary palliative care clinical practice [ISRCTN81117481]. *BMC Palliat Care*. 2005;4(1):7. doi:10.1186/1472-684X-4-7

22. EuroQol Group. EuroQol–a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208. doi:10.1016/0168-8510(90)90421-9

23. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care*. 1991;7(2):6-9. doi:10.1177/082585979100700202

24. US Department of Health and Human Services; National Institutes of Health; National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE): version 4.0. Published May 28, 2009. Accessed October 24, 2022. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

25. Johnson MJ, Bland JM, Oxberry SG, Abernethy AP, Currow DC. Clinically important differences in the intensity of chronic refractory breathlessness. *J Pain Symptom Manage*. 2013;46(6):957-963. doi:10.1016/j.jpainsymman.2013.01.011

26. Ekström M. Why treatment efficacy on breathlessness in laboratory but not daily life trials? the importance of standardized exertion. *Curr Opin Support Palliat Care*. 2019;13(3):179-183. doi:10.1097/SPC.0000000000000444

27. Bruera E, MacEachern T, Ripamonti C, Hanson J. Subcutaneous morphine for dyspnea in cancer patients. *Ann Intern Med*. 1993;119(9):906-907. doi:10.7326/0003-4819-119-9-199311010-00007

28. Parshall MB, Schwartzstein RM, Adams L, et al; American Thoracic Society Committee on Dyspnea. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*. 2012;185(4):435-452. doi:10.1164/rccm.201111-2042ST