Morphine for chronic breathlessness (MABEL) in the UK: a multi-site, parallel-group, dose titration, double-blind, randomised, placebo-controlled trial

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Summary

Background **The effectiveness of opioids for breathlessness seen in laboratory-based studies has not been replicated in clinical trials. We aimed to assess the effectiveness of oral morphine for breathlessness in long-term conditions.**

Methods **This phase 3, parallel-group, double-blind, placebo-controlled trial across 11 centres randomly assigned consenting adults (1:1, stratified by site and causal disease) with a modified Medical Research Council breathlessness score of 3 or more due to cardiorespiratory conditions to receive 5–10 mg twice daily oral long-acting morphine or placebo (as well as a blinded laxative) for 56 days. The primary outcome was worst breathlessness score in the past 24 h at day 28, measured using a numerical rating scale (NRS; 0=not breathless at all; 10=worst imaginable breathlessness). Secondary outcomes included physical activity levels, worst cough NRS, quality of life, and morphine-related toxicities. Patients who received at least one dose of study drug were eligible for inclusion in efficacy and safety analyses. The trial was registered with ISRCTN (ISRCTN87329095) and the EU Clinical Trials Register (EudraCT 2019-002479-33).**

Findings **Between March 18, 2021, and Oct 26, 2023, 143 participants were randomly assigned to receive either morphine (73 participants) or placebo (67 participants) and were included in the analyses; three participants did not receive the allocated treatment. Participants had a mean age of 70·5 (SD 9·4) years, were mostly male (93 [66%]), and were mostly White (132 [94%]). By day 28, 64 (88%) participants in the morphine group versus 66 (99%) in the placebo group had 90% adherence or greater. We found no evidence of difference in worst breathlessness at day 28 (morphine 6·19 [95% CI 5·57 to 6·81] *vs* placebo 6·10 [5·44 to 6·76]; adjusted mean difference 0·09 [95% CI –0·57 to 0·75], p=0·78) or any secondary measure, except for improved cough seen at day 56 (adjusted mean difference –1·41 [–2·18 to –0·64]). Increased moderate to vigorous physical activity was seen at day 28 (adjusted mean difference 9·51 min/day [0·54–18·48]) but this was not significant after multiple-measures correction. The morphine group had more adverse events (251 *vs* 162), serious adverse events (15 *vs* three, of which three in the morphine group and zero in the placebo group were deemed to be related to the study), and study drug withdrawals (13 *vs* two). There were no treatment-related deaths.**

Interpretation **We found no evidence that morphine improves worst breathlessness intensity. Further research is needed to understand whether there is any role for morphine in chronic breathlessness, but our findings do not support its use in this setting.**

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See **Online** for appendix

Introduction

Chronic or persistent breathlessness is frightening, disabling, and is prevalent in many chronic conditions, particularly cardiorespiratory diseases and cancer.[1,2] From the prevalence of chronic respiratory diseases alone, over 450 million people globally, the large burden of chronic breathlessness is clear.[3] Breathlessness is closely related to physical exertion and is associated with reduced quality of life and higher unscheduled health-service use and costs.[4,5] Despite evidence-based breathlessness-targeted interventions,[6] this devastating symptom is often neglected and implementation of clinical guidelines is low.[7]

There is a good rationale to use opioids to treat chronic breathlessness. Breathlessness perception is processed in brain areas that are rich in opioid receptors.[8] Exertion-induced breathlessness is reduced by endogenous opioids but increased by opioid antagonism.[9] Exercise laboratory studies with isotime and load exercise tests show improved breathlessness and exercise endurance with opioids in studies with both healthy volunteers and people living with chronic breathlessness.[6,9] Neuroimaging studies indicate central modulation of breathlessness perception pathways.[8] A repeat-dose clinical study of morphine in people with breathlessness at rest showed a clinical and statistically significant benefit.[10] However, clinical trials in

Research in context

Evidence before this study

Opioids, and particularly morphine, have the largest body of literature investigating their management potential for breathlessness. Exercise laboratory, mainly single-dose, studies including standardised exercise testing of short-acting opioids showed breathlessness reduction and increased exercise endurance. A 7-day clinical trial of repeat-dose, long-acting morphine showed benefit in people with very severe chronic breathlessness (breathless at rest). However, adequately powered clinical trials in ambulatory patients have not shown improved chronic breathlessness at 7 days, although subgroup analyses have indicated benefits for people with the most severe breathlessness. The only adequately powered trial of long-acting morphine for a longer period (4 weeks) showed benefit for the primary endpoint (Chronic Obstructive Pulmonary Disease [COPD] Assessment Test). In this study, improved breathlessness was seen only in those with moderate to severe breathlessness (modified Medical Research Council breathlessness scale [mMRC] ≥3). To our knowledge, no daily life clinical trials included a standardised exercise test and therefore improvements in exercise endurance might have been undetected. We searched MEDLINE (Jan 1, 2000–May 31, 2024; systematic reviews, English language) using the terms "dyspn* OR breath*" AND "opioid" OR "morphine"; no formal appraisal of quality was undertaken. The most recent systematic review of opioids for breathlessness (only COPD, 24 studies, 975 participants) confirmed overall benefit for breathlessness, but subgroup meta-analysis by study design (crossover, mostly single-dose with standardised exercise test *vs* parallel-group, repeat-dose without standardised exercise test) showed benefit in the crossover studies, but not in the parallel-group trials. Regarding safety, there are excess harms with morphine compared with placebo, but most are mild, self-limiting, and occur during the first week of treatment or following dose titration (consistent with morphine's profile). Respiratory depression is reported, but rarely under clinical trial conditions. The 2024 European Respiratory Society guidelines for symptom management in people with non-malignant respiratory disease made a cautious recommendation against the use of opioids, citing low-level evidence and high uncertainty in the daily life clinical trials.

Added value of this study

This study is the first adequately powered 4-week trial of the effectiveness and safety of low-dose, long-acting morphine for moderate to severe (mMRC ≥3) chronic breathlessness caused by various conditions (mainly respiratory), including the largest dataset reporting objective daily physical activity profiles. We found no benefit in the primary outcome measure of self-reported breathlessness intensity but some evidence of benefit in secondary outcome measures. These outcomes included an indication of improved physical activity levels (non-significant after multiple-measures correction) and improved cough (significant) in the context of lower toxicity and a much higher adherence rate than previously reported trials. There was no difference in some common morphine-related concerns such as sedation or cognitive impairment, although there was excess study drug withdrawal in the morphine arm. To our knowledge, this is the first study to incorporate a lower starting dose (10 mg/24 h *vs* 20 mg/24 h) alongside a clinician training programme to manage common adverse effects, providing a template for safer use in practice.

Implications of all the available evidence

The findings from this trial of long-acting morphine confirm the findings of previous work showing no difference in self-reported worst breathlessness recalled over the past 24 h. Further research is required to explore if morphine might increase exercise endurance, how this can translate to daily moderate physical activity, and if morphine improves cough. Future studies should be designed with primary outcomes relating to exercise endurance (eg, breathlessness measured at isotime and isoload), physical activity, and cough to fully understand if morphine has any role for people living with chronic breathlessness.

ambulant populations did not show benefits of opioids for breathlessness-related primary outcomes.[6] These trials had no measure of exercise endurance, although one sub-study of physical activity suggested a reduction in sedentary activity.[11] In addition, there are few data on people with interstitial lung disease, although the data that do exist show a signal of benefit of opioids for chronic breathlessness.[12,13]

The MABEL trial aimed to assess the effectiveness, cost-consequences, and safety of long-acting, low-dose, oral morphine over 4 weeks for the reduction of breathlessness in people with moderate to severe breathlessness due to long-term conditions. Secondary objectives included comparing the amount and level of physical activity, morphine-related toxicity, other symptom intensity, and quality of life.

Methods

Study design and participants

MABEL was a UK-based, phase 3, double-blind, parallel-group, pragmatic randomised controlled trial, with an embedded normalisation process theory-based sub-study and a study within a trial (evaluating the use of an infographic sheet on participant recruitment). We report our methods and results according to the CONSORT statement pragmatic trial extension.[14] The implementation sub-study is available as a preprint,[15] and the study within a trial will contribute to future meta-analyses. The protocol is published (appendix pp 25–101).[16]

The trial protocol and amendments were approved by the North East–Tyne and Wear South Research Ethics Committee (19/NE/0284) and by the Medicines and Healthcare Products Regulatory Agency. The trial was sponsored by Hull University Teaching Hospitals NHS Trust and conducted by Hull Health Trials Unit. Edinburgh Clinical Trials Unit conducted the statistical and health economic analyses. The trial was registered with ISRCTN (ISRCTN87329095) and the EU Clinical Trials Register (EudraCT 2019-002479-33).

Eligible patients from 11 centres were consenting, ambulant adults over the age of 18 years with moderate to severe chronic breathlessness (modified Medical Research Council breathlessness scale[17] [mMRC] grade ≥3, assessed by site physician) due to cardiac disease, respiratory disease, post-COVID-19, or cancer, whose management of the underlying condition had been unchanged for the previous 7 days. All participants must also have been able to complete the trial assessments and questionnaires. Those with known contraindications to morphine, an Australia-modified Karnofsky Performance Scale (AKPS)[18] score of less than 40 (in bed >50% of the time), or an estimated glomerular filtration rate (eGFR) of less than 25 mL/min per 1·73² (<30 mL/min if heart failure), or who had used opioid medications containing more than 5 mg morphine-equivalents daily for any more than 7 of the last 14 days were excluded. Other opioids, or benzodiazepines greater than 20 mg diazepam daily equivalents, were not permitted. If a participant required a strong opioid for clinical care, they were withdrawn from study drug but could continue providing data. Patients with childbearing potential could partake only if they agreed to use adequate contraception during the study and for 7 days after cessation. Potential participants were identified through site clinicians (inpatient, outpatient, community) in oncology, respiratory, rehabilitation, cardiology, palliative care services, and through clinical databases.

Informed consent was taken before baseline data collection (face-to-face, telephone or video, electronic or postal[16]). Participants were invited to identify someone who provided support, usually a family member. This person was approached to consent to provide carer burden data, which will be presented in an upcoming report.

Randomisation and masking

After baseline data collection, participants were randomly assigned 1:1 in randomly permuted blocks using the REDCapCloud system, stratified by dominant disease causing the breathlessness (site clinician assessed) and site. Participants received either twice daily oral 5 mg morphine sulfate modified release and 100 mg twice daily oral docusate sodium or placebo morphine and placebo laxative. The dose regimen was based on a previous dose titration and pharmacovigilance study, and high morphine-related attrition in previous trials started at 20 mg daily.[19] On-site pharmacies at the included centres were notified of blinded randomisation allocation using an access-restricted form. Morphine, docusate, and corresponding placebo capsules were over-encapsulated with identical taste, smell, and consistency. Participants, investigators, and clinicians were masked to group allocation. An independent unblinded statistician conducted activities requiring knowledge of the group allocation. Regular monitoring was conducted by Hull Health Trials Unit on behalf of the sponsor, and no risk of unblinding was found.

Procedures

At least two site clinicians completed morphine prescribing training (including management of common side-effects) before recruitment. On day 7 after baseline data collection, a dose titration assessment was made. Participants with a less than one-point improvement from baseline in the primary outcome (0–10 numerical rating scale [NRS] of worst breathlessness in the past 24 h) and acceptable harms increased their dose to 10 mg (or corresponding placebo) twice daily from day 15. Acceptable harms were defined as either (1) no side-effects, or (2) no new or worse gastrointestinal effects at grade 3 or above (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]), or (3) no new or worse neurocognitive harms of any grade.

Participants wore an ActiGraph activity monitor for 7 days before randomisation (day –8 to day 0) and before the primary endpoint (days 20–28). Evaluable data were counted as data from participants with at least 33% wear time per day for at least 3 valid days.[20] Activity measures included average daily step count, active calories, metabolic rate, and time spent in sedentary, light, or moderate and vigorous activity. Subjective sleepiness was measured using the Karolinska Sleepiness Scale (KSS[21]) and cognitive function assessed using the Saint Louis University Mental Status (SLUMS[22]) examination. Participants completed the Subjective Opioid Withdrawal Scale (SOWS) 3 days after stopping study treatment.[23] We systematically monitored symptoms known to be associated with morphine use, hereafter referred to as morphine-related harms. Common morphine-related harms (constipation, nausea, vomiting, sedation, and cognitive disturbance) were monitored using the NCI-CTCAE grading at days 2 and 4 (and days 16 and 18 if dose escalated) and managed by site clinicians if reported. Neurocognitive disturbance (cognition, memory, hallucinations, NCI-CTCAE grade 1 or above; vivid dreams new or worse since baseline; somnolence ≥8 on the KSS[21]) or gastrointestinal effects (constipation, nausea, vomiting) with CTCAE grade ≥2 were reported as adverse events. Grade 3 events not improving with management or grade 4 events necessitated the withdrawal of the study drug.

Assessments were conducted at baseline and at days 2, 4, 7, 14 (and days 16 and 18 if dose escalated), 28, and 56 after the start of treatment (appendix pp 36–38). Demographic characteristics (age, disease stage, BMI, previous medical history, eGFR result) were recorded from medical records and self-reported mMRC breathlessness score, self-reported sex (male, female, and other), and self-reported ethnicity were recorded at baseline only. Vital signs (pulse and respiratory rate, blood pressure, pulse oximetry, and transcutaneous CO_2 [if available]) were measured at baseline and day 28. The Health Resource Utilisation questionnaire, based on the UK Cancer Costs questionnaire, was used to measure health-service use. Study medication adherence was recorded at study visits and study drug accountability at each dispensing visit.

For more on the **UK Cancer Costs questionnaire** see https://blogs.ed.ac.uk/ukcc/

Outcomes

The primary outcome was self-reported worst breathlessness over the past 24 h at day 28, measured with an 11-point NRS (0=not breathless at all; 10=worst imaginable breathlessness).[24] Secondary outcomes were worst breathlessness at all other timepoints (to day 56); average distress due to breathlessness, pain, and cough over the past 24 h (11-point NRSs [0–10]; all timepoints to day 56); daytime sleepiness (Epworth Sleep Questionnaire; days 28 and 56);[25] functional status (AKPS; days 28 and 56);[18] health-related quality of life (SF-12; days 28 and 56);[26] health status (EQ-5D-5L; days 28 and 56);[27] capability (ICECAP-SCM; days 28 and 56);[28] physical activity (ActiGraph; day –8 to day 0; days 20–28);[20] and morphine-related harms including KSS (all timepoints to day 56; appendix p 36).

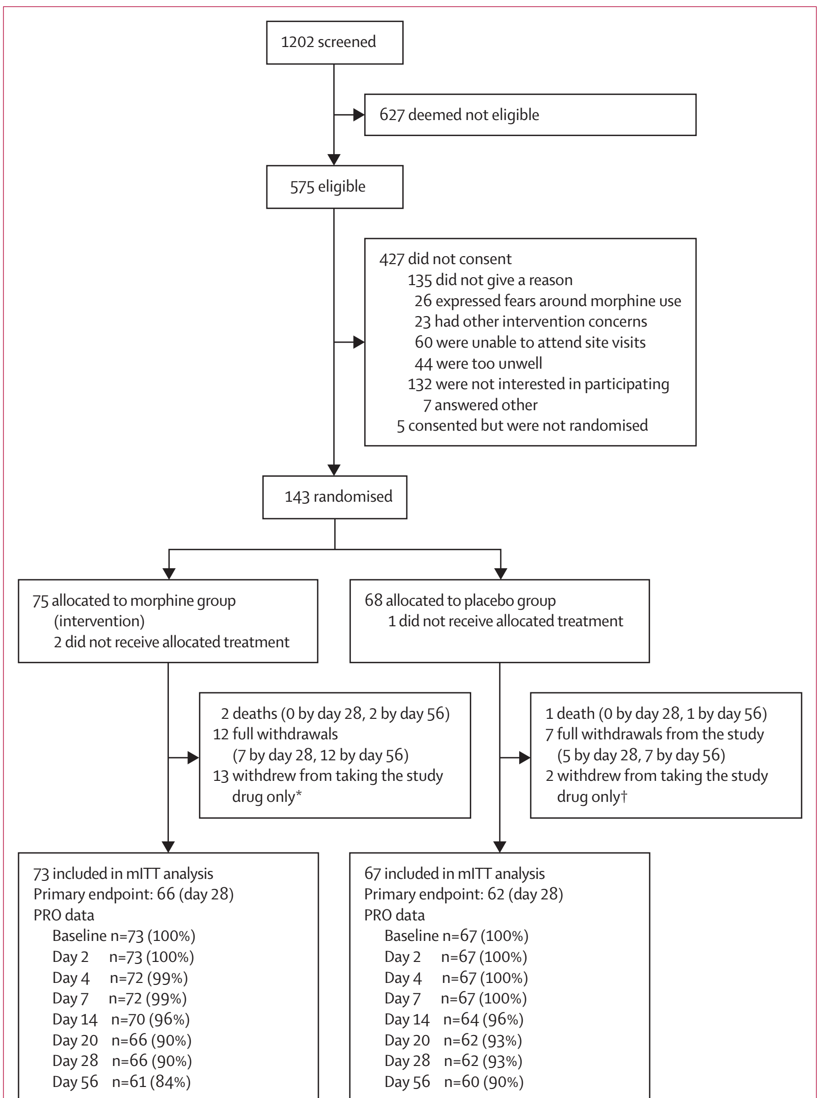

Figure 1: **Trial profile**
We were unable to collect data on reasons participants were deemed ineligible. mITT=modified intention-to-treat. PRO=patient-reported outcome. *Six withdrew due to treatment toxicity, five were unwilling to continue treatment, and two withdrew for other reasons. †One withdrew due to treatment toxicity, and one was unwilling to continue treatment.

The safety endpoints were adverse reactions, serious adverse events, suspected unexpected serious adverse events (SUSARS), and deaths up to 84 days after treatment started. Serious adverse events were adjudicated by the principal investigator of the site and MABEL's chief investigator, but the chief investigator was not permitted to downgrade the severity as assessed by the site principal investigator.

Statistical analysis

To detect a one-point change in NRS (moderate effect size 0·4) in the primary outcome of worst breathlessness in the past 24 h at day 28, a sample size of 126 patients overall (63 participants per group) was required.[29] This calculation was based on assuming an SD of 2·5, a correlation of 0·5 between post-randomisation measures, and adjustment for baseline covariates (assuming a correlation with outcome of 0·5), for 90% power and a 5% level of significance. Allowing for 20% attrition required an increase to 158 participants (79 participants per group).

Primary and sensitivity analysis of the primary endpoint (day 28) was performed on a modified intention-to-treat (mITT) population consisting of randomised participants who received at least one dose of the study drug. The safety population was the same.

The primary analysis used a repeated measures mixed-effects analysis of covariance including terms for treatment, time, and breathlessness measurements as fixed effects. The stratification variables (site as a random effect and causal disease as a fixed effect) were included and the model adjusted for baseline worst breathlessness (fixed effect). The model also included a treatment-by-time interaction. An autoregressive covariance structure was used in the model, which assumed correlation to be highest between adjacent times. The repeated measures analysis enabled the estimation of a treatment effect at day 28 and an overall assessment of the treatment effect over the 56-day outcome period, taking into consideration worst breathlessness measured across all timepoints. For the primary analysis, a two-sided $p<0·05$ was regarded as significant.

Secondary outcomes measured at multiple timepoints were analysed using the repeated measures approach described for the primary outcome. Where outcomes were not measured repeatedly, analyses were

	Morphine (n=73)	Placebo (n=67)
Age, years	70·6 (10·2)	70·3 (8·4)
Sex		
Male	48 (66%)	45 (67%)
Female	25 (34%)	22 (33%)
Ethnicity or origin		
White	69 (95%)	63 (94%)
Asian or Asian British	2 (3%)	2 (3%)
Black, African, Caribbean, or Black British	2 (3%)	1 (1%)
Other ethnic origin	0	1 (1%)
Primary diagnosis		
COPD	40 (55%)	37 (55%)
Other non-malignant lung disease	30 (41%)	30 (45%)
Heart disease	3 (4%)	0
Cancer	1 (1%)	0
BMI, kg/m²	27·1 (6·4)	27·4 (5·1)
eGFR, mL/min per 1·73 m²	70·5 (16·7)	69·9 (19·1)
Systolic blood pressure, mm Hg	132·2 (20·5)	131·3 (23·3)
Diastolic blood pressure, mm Hg	74·8 (10·4)	75·1 (12·0)
Resting pulse, beats per min	80·29 (13·0)	79·39 (14·6)
Resting respiration rate, breaths per min	20·59 (3·9)	20·01 (4·2)
Pulse oximetry oxygen saturation, %	93·84 (3·4)	94·33 (2·6)
Comorbidities		
0	3 (4%)	1 (1%)
1	15 (21%)	15 (22%)
At least 2	55 (75%)	51 (76%)
mMRC breathlessness score		
mMRC 1	0	1 (1%)
mMRC 2	4 (5%)	1 (1%)
mMRC 3	50 (68%)	43 (64%)
mMRC 4	19 (26%)	22 (33%)
AKPS		
50: considerable assistance, frequent medical care	4 (5%)	5 (7%)
60: occasional assistance, can care for most needs	29 (40%)	26 (39%)
70: cares for self, cannot carry on normal activity or work	27 (37%)	25 (37%)
80: normal activity with effort, some signs or symptoms	11 (15%)	8 (12%)
90: normal activity, minor signs or symptoms	1 (1%)	2 (3%)
100: normal; no complaints, no evidence of disease	1 (1%)	1 (1%)
NRS worst breathlessness	6·8 (1·5)	6·8 (1·9)
NRS distress due to breathlessness	5·3 (2·6)	5·1 (2·8)
NRS most severe cough	4·5 (2·9)	3·9 (2·7)
NRS pain	3·0 (2·8)	2·7 (2·8)
SF-12		
Physical component	31·4 (6·5)	31·2 (6·3)
Mental component	49·3 (10·1)	44·4 (10·8)
ICECAP-SCM	0·64 (0·14)	0·67 (0·12)
EQ-5D-5L	0·60 (0·19)	0·56 (0·23)
EQ-VAS	55 (16)	48 (21)
Epworth Sleep Scale	6·5 (4·9)	7·4 (5·4)
Karolinska Sleepiness Scale	6·5 (4·9)	7·4 (5·4)
SLUMS questionnaire	24·9 (4·1)	25·1 (3·2)
Average daily step count*	6824 (2562)	7189 (3454)
Total time in moderate or vigorous activity, min/day	54 (39)	65 (56)

(Table 1 continues in next column)

(Continued from previous column)

Data are mean (SD) or n (%). AKPS=Australia-modified Karnofsky Performance Scale. COPD=chronic obstructive pulmonary disease. eGRF=estimated glomerular filtration rate. EQ-5D-5L=EuroQol 5-Dimension 5-Level Version. EQ-VAS=EuroQol Visual Analogue Scale. ICECAP-SCM=Icepop Capability Supportive Care Measure. mMRC=modified Medical Research Council. NRS=numerical rating scale. SF-12=12-item Short-Form Health Survey. SLUMS=Saint Louis University Mental Status. *Actigraphy monitor worn on non-dominant wrist.

Table 1: **Baseline characteristics**

undertaken using the appropriate version of the generalised linear model (eg, linear for continuous outcomes, logistic for binary outcomes, or Poisson for count data). As with the primary outcome, analyses were adjusted for stratification variables and the relevant baseline variable. We adjusted for multiple comparisons across the secondary outcomes using a Bonferroni approach assuming a family of 25 relevant comparisons across the secondary outcomes and multiple times, so the working significance level for interpreting the secondary outcome tests was 0·002 (0·5 divided by 25). We present unadjusted p values unless otherwise stated. Safety reporting details were prespecified in the statistical analysis plan (appendix pp 102–113) before data lock.

A sensitivity analysis was conducted with imputed missing primary outcome data taking into consideration assumptions such as missing at random or missing not at random depending on reasons for missingness. The imputation method was model-based and made use of the stratification variables as part of the imputation model.

To account for non-adherence, a complier average causal effect analysis was planned as a sensitivity analysis. Treatment adherence was assumed to be binary with a clinically relevant adherence of 70% or greater used to define whether a patient is adherent or non-adherent.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Adjusted mean (95% CI)		Adjusted mean difference (95% CI)	p value†
	Morphine (n=73)*	Placebo (n=67)*		
Worst breathlessness (NRS 0–10)				
Day 28	6·19 (5·57–6·81)	6·10 (5·44–6·76)	0·09 (–0·57 to 0·75)	0·78
Day 56	61·7 (5·5–6·8)	64·2 (57·6–70·9)	–0·26 (–0·93 to 0·42)	0·45
Overall effect	59·9 (54·8–64·9)	61·9 (56·4–67·3)	–0·20 (–0·60 to 0·20)	0·32
Average daily steps‡	6753 (6100–7406)	6509 (5787–7232)	243·2 (–244 to 730·4)	..
SLUMS questionnaire‡	24·9 (23·4–26·4)	25·1 (23·5–26·8)	–0·25 (–1·32 to 0·82)	..
Levels of physical activity (min/day)				
Sedentary‡	704 (629–780)	726 (642–809)	–21·4 (–78·1 to 35·30)	..
Light‡	487 (448–526)	475 (431–518)	11·96 (–17·4 to 41·34)	..
Moderate to vigorous‡	63·0 (50·9–75·0)	53·4 (40·2–66·7)	9·51 (0·54 to 18·48)	..
Average active calories‡	952 (838–1066)	894 (769–1020)	57·67 (–27·9 to 143·2)	..
Average MET rate‡	1·24 (1·14–1·34)	1·27 (1·16–1·38)	–0·03 (–0·10 to 0·04)	..
Breathlessness distress (NRS 0–10)				
Day 28	4·21 (3·29–5·13)	3·64 (2·64–4·63)	0·57 (–0·36 to 1·50)	..
Day 56	3·77 (2·84–4·70)	4·31 (3·31–5·30)	–0·54 (–1·47 to 0·40)	..
Overall effect	3·76 (2·97–4·56)	3·59 (2·72–4·46)	0·18 (–0·45 to 0·80)	..
Worst cough (NRS 0–10)				
Day 28	3·05 (2·32–3·78)	3·41 (2·60–4·21)	–0·36 (–1·11 to 0·40)	..
Day 56	2·53 (1·78–3·28)	3·94 (3·13–4·75)	–1·41 (–2·18 to –0·64)	..
Overall effect	2·79 (2·16–3·42)	3·49 (2·78–4·19)	–0·70 (–1·22 to –0·17)	..
Average pain (NRS 0–10)				
Day 28	1·76 (0·95–2·56)	1·91 (1·03–2·80)	–0·16 (–0·97 to 0·66)	..
Day 56	1·94 (1·12–2·77)	2·11 (1·22–2·99)	–0·17 (–0·99 to 0·66)	..
Overall effect	1·78 (1·07–2·49)	2·19 (1·40–2·98)	–0·41 (–1·01 to 0·18)	..
Epworth Sleep Scale				
Day 28	6·18 (4·89–7·48)	5·98 (4·55–7·41)	0·20 (–0·98 to 1·38)	..
Day 56	5·44 (4·11–6·77)	5·37 (3·93–6·80)	0·07 (–1·12 to 1·27)	..
Overall effect	5·81 (4·57–7·05)	5·67 (4·31–7·04)	0·14 (–0·88 to 1·15)	..
Karolinska Sleepiness Scale				
Day 28	3·11 (2·58–3·64)	3·21 (2·66–3·76)	–0·10 (–0·63 to 0·43)	..
Day 56	3·20 (2·65–3·74)	3·07 (2·51–3·64)	0·12 (–0·43 to 0·68)	..
Overall effect	3·28 (2·86–3·71)	3·28 (2·83–3·73)	0·01 (–0·28 to 0·29)	..
AKPS				
Day 28	69·4 (66·2–72·7)	70·8 (67·3–74·4)	–1·41 (–4·40 to 1·59)	..
Day 56	69·9 (66·6–73·2)	69·9 (66·3–73·5)	0·01 (–3·05 to 3·07)	..
Overall effect	69·7 (66·6–72·7)	70·4 (67·0–73·7)	–0·70 (–3·15 to 1·75)	..
SF-12 physical subscale				
Day 28	33·7 (31·1–36·4)	34·1 (31·2–37·0)	–0·39 (–2·58 to 1·79)	..
Day 56	33·1 (30·4–35·8)	33·9 (31·0–36·8)	–0·80 (–3·02 to 1·42)	..
Overall effect	33·4 (30·9–36·0)	34·0 (31·2–36·8)	–0·60 (–2·46 to 1·27)	..
SF-12 mental subscale				
Day 28	49·7 (46·5–52·9)	48·7 (45·3–52·2)	0·97 (–1·99 to 3·93)	..
Day 56	49·0 (45·7–52·3)	47·6 (44·2–51·1)	1·38 (–1·62 to 4·39)	..
Overall effect	49·4 (46·4–52·4)	48·2 (44·9–51·5)	1·17 (–1·32 to 3·67)	..

(Table 2 continues on next page)

Results

Between March 18, 2021, and Oct 26, 2023, 148 patients consented and 143 were randomly assigned to receive either morphine (75 participants) or placebo (68 participants; figure 1). Nearly all participants randomised to morphine (73 [97%] of 75) and the placebo group (67 [99%] of 68) received at least one dose of the allocated treatment and formed the mITT group (n=140). Participants had a mean age 70·5 (SD 9·4) years, 132 (94%) of the 140 participants self-reported as being White, and 93 (66%) were men (table 1). All participants were assessed by the site physician as having an mMRC breathlessness score of 3 or more at enrolment, and 134 (97%) participants self-reported an mMRC breathlessness score of 3 or more at baseline. All participants except four (3%) had at least one comorbidity, and breathlessness was mainly due to chronic lung disease (table 1, appendix p 6).

Before day 56, 13 (18%) of 73 participants in the morphine group and two (3%) of 67 in the placebo group withdrew from taking the study drug but continued to provide data on all outcomes and safety. Three participants (two [3%] of 73 in the morphine group and one [1%] of 67 in the placebo group) died before day 56.

Morphine was well-tolerated, with adherence greater than or equal to 90% at day 28 for 64 (88%) of 73 participants versus 66 (99%) of 67 in the placebo group (appendix pp 10–11). Overall, about a third of participants (21 [29%] in the morphine group and 24 [36%] in the placebo group) dose-escalated at day 15 (appendix p 11).

There was no evidence of a meaningful difference in worst breathlessness (NRS) score at day 28 between morphine and placebo (morphine 6·19 [95% CI 5·57 to 6·81] *vs* placebo group 6·10 [5·44 to 6·76]; adjusted mean difference 0·09 [95% CI –0·57 to 0·75], p=0·78; table 2, appendix p 12). The lower 95% CI rules out a prespecified clinically important change of –1 point.

There was no meaningful difference in worst breathlessness (NRS) score at other timepoints (figure 2, appendix p 12) and no evidence of a difference at day 28 for distress due to breathlessness, pain, cough, daytime sleepiness or sedation, cognitive function, functional status, or health-related quality of life or capability (appendix pp 13–20). However, by day 56, there was evidence of improvement for cough in the morphine group compared with placebo (morphine 2·53 [1·78–3·28] *vs* placebo 3·94 [3·13–4·75]; adjusted mean difference –1·41 NRS points [–2·18 to –0·64]; appendix p 14). For these exploratory secondary outcomes, unadjusted p values are shown in the relevant appendix tables with the adjusted level of significance (p=0·002) stated for interpretation.

Evaluable actigraphy data were provided by 129 (92%) of 140 participants at baseline, and 113 (81%) of 140 at day 28. With the point estimates, there were increased average daily steps and calorie expenditure, and a reduction in sedentary activity in the morphine group (appendix pp 16–17). There was also an increase in time spent in moderate to vigorous activity in the morphine compared with the placebo group (morphine 63·0 min/day [95% CI 50·9–75.0] *vs* placebo 53·4 min/day [40·2–66·7]; adjusted mean difference 9·51 min [0·54–18·48]). The findings, however, are imprecise, with wide CIs.

There were 413 adverse events recorded to day 56—251 events in 63 morphine participants and 162 events in 51 placebo participants (table 3). Fewer were attributed as unlikely to be related or not related to the study in the morphine group (148 [59%]) versus the placebo group (128 [79%]). Morphine-related adverse events were more common in the morphine group. Of all adverse events, vivid dreams (29 [12%] *vs* 14 [9%]), nausea (21 [8%] vs six [4%]), vomiting (eight [3%] vs two [1%]), and constipation (28 [11%] *vs* three [2%]) were more common in the morphine group (appendix pp 21–22). There were 18 serious adverse events in 16 participants, all resulting in hospitalisation (table 4). 15 were recorded in the morphine group (12 [80%] unlikely to be related or not related to the study) and three in the placebo group (three [100%] unlikely to be related or not related to the study; table 2, appendix p 19, 23). Categorisation of serious adverse events during the blinded phase attributed two to the study, both in the morphine arm. However, on review of the clinical details after unblinding, we included a further serious adverse event to make three morphine-related serious adverse events in total. This third serious adverse event was categorised by the site clinician as unlikely to be related to the study, but the cause of admission was constipation (appendix p 23).

Three participants had serious adverse events resulting in death before day 56. Two (66%) deaths were in the morphine group (chest infection and myocardial infarction) and one (33%) was in the placebo group (congestive cardiac failure). No death was attributed to study medication by the site investigator. There were no SUSARs and no episodes of respiratory depression. Despite a non-significant numerical increase in physical activity in the morphine group, there were no excess falls (one of 73 in the morphine group *vs* one of 67 in the placebo group). Overall, six (8%) of 73 participants had moderate opioid withdrawal and two (5%) had severe opioid withdrawal symptoms, compared with none in the placebo arm (appendix p 16). There was no apparent difference in mild symptoms of withdrawal between arms (morphine 27 [37%] of 73 *vs* 26 [39%] of 67; appendix p 16).

Protocol deviations occurred approximately equally across the allocated groups (appendix p 10). Most were related to data collection issues (visits not being completed within the time window, missing questionnaires, etc) or to study drug administration or adherence checking (missed doses, bottles not returned, etc).

	Adjusted mean (95% CI)		Adjusted mean difference (95% CI)	p value†
	Morphine (n=73)*	Placebo (n=67)*		
(Continued from previous page)				
EQ-VAS				
Day 28	51·2 (44·8–57·6)	46·2 (39·2–53·3)	4·93 (–0·95 to 10·81)	··
Day 56	52·1 (45·5–58·6)	48·6 (41·6–55·7)	3·42 (–2·55 to 9·39)	··
Overall effect	51·6 (45·5–57·7)	47·4 (40·8–54·1)	4·18 (–0·74 to 9·10)	··
EQ-5D-5L				
Day 28	0·66 (0·60–0·72)	0·62 (0·55–0·68)	0·04 (–0·01 to 0·09)	··
Day 56	0·65 (0·59–0·71)	0·64 (0·58–0·70)	0·01 (–0·04 to 0·07)	··
Overall effect	0·66 (0·60–0·71)	0·63 (0·57–0·69)	0·03 (–0·01 to 0·07)	··
ICECAP-SCM				
Day 28	0·63 (0·59–0·68)	0·67 (0·63–0·72)	–0·04 (–0·08 to 0·00)	··
Day 56	0·62 (0·57–0·68)	0·66 (0·62–0·70)	–0·04 (–0·09 to 0·01)	··

The repeated measures analysis (where appropriate) not only enabled the estimation of a treatment effect at day 28 and day 56, but also allowed for an overall assessment of the treatment effect during the 28-day outcome period—eg, taking into consideration worst breathlessness measured across all prespecified timepoints. AKPS=Australia-modified Karnofsky Performance Scale. EQ-5D–5L=EuroQol 5-Dimension 5-Level version. EQVAS=EuroQol Visual Analogue Scale. ICECAP-SCM=Icepop Capability Supportive Care Measure. MET=metabolic equivalent of task. NRS=numerical rating scale. SF–12=12-item Short-Form Health Survey. SLUMS=Saint Louis University Mental Status.
*At day 28, morphine (n=66) and placebo (n=62). At day 56, morphine (n=61) and placebo (n=60). †p values shown for the primary outcome only (p values shown in the appendix [pp 13–20] with a significance level corrected for multiple measures of p=0·002 to preserve the overall notional level of significance of 0·05 across the secondary outcomes). ‡Only measured at day 28, so value is both the day 28 result and the overall effect.

Table 2: **Primary and secondary outcomes**

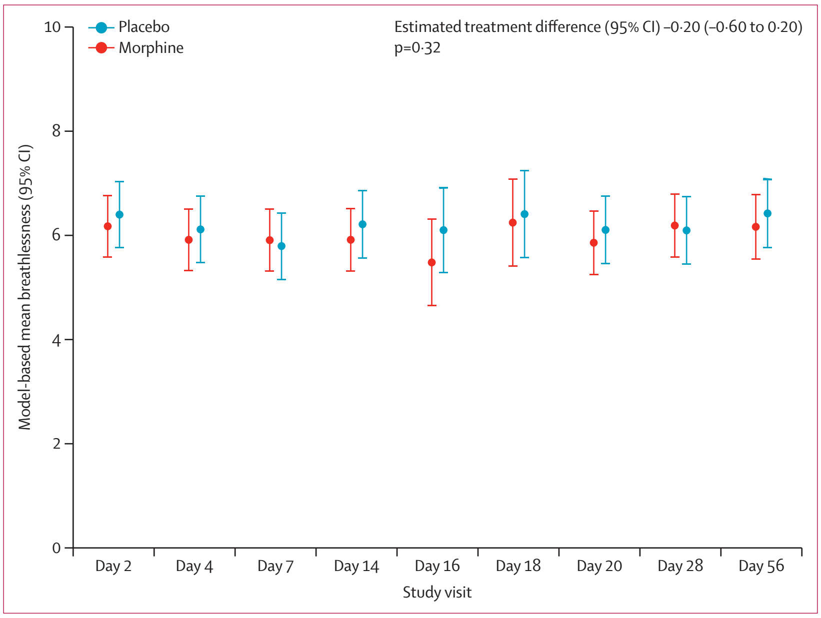

Figure 2: **Model adjusted means with 95% CIs for the primary outcome (worst breathlessness in past 24 h at day 28)**
Breathlessness scale: 0=not breathless at all; 10=worst imaginable breathlessness. The treatment difference and p value presented relate to the overall effect across all timepoints.

The pre-planned complier average causal effects analysis was not undertaken as adherence was higher than anticipated. The sensitivity analysis to assess the effect of the differential missing data patterns,

	Morphine (n=73)	Placebo (n=67)
Total number of adverse events	251	162
Number of participants with at least one adverse event	63 (86%)	51 (76%)
Number of adverse events per participant		
1	11 (17%)	16 (31%)
2	8 (13%)	9 (18%)
3	16 (25%)	13 (25%)
4	11 (17%)	3 (6%)
5	4 (6%)	2 (4%)
6	4 (6%)	3 (6%)
7	3 (5%)	1 (2%)
8	1 (2%)	1 (2%)
9	1 (2%)	1 (2%)
10	0	0
11	1 (2%)	1 (2%)
12	1 (2%)	0
13	1 (2%)	0
14	1 (2%)	1 (2%)
Total number of serious adverse events*	15	3
Number of participants with at least one serious adverse event	13 (87%)	3 (21%)
Number of serious adverse events per participant		
1	11 (73%)	3 (100%)
2	2 (13%)	0
Number of deaths	2 (3%)	1 (1%)
Serious adverse events by MedDRA term		
Cardiac conditions	1 (1%)	1 (1%)
Infections and infestations	4 (5%)	0
Injury, poisoning†, and procedural complications	1 (1%)	1 (1%)
Respiratory, thoracic, and mediastinal conditions	5 (7%)	1 (1%)
Gastrointestinal disorders	2 (3%)	0
Renal and urinary disorders	1 (1%)	0

MedDRA=Medical Dictionary for Regulatory Activities. *Serious adverse events include both those with expedited reporting and those that did not require this according to the protocol. †There were no poisonings.

Table 3: **Safety and reporting of adverse events**

assuming missing data were not randomly distributed, supported the primary analysis (appendix p 12).

Discussion

At day 28, we found no meaningful evidence of between-group difference in the primary endpoint of worst breathlessness over the previous 24 h, or for any other outcome. There was a numerical increase in time spent in moderate or vigorous physical activity, although this finding was no longer statistically significant following correction for multiple measures. By day 56, there was some evidence of improved cough in the morphine group. There were more adverse events in the morphine group, but these were mainly mild and related to the first treatment week or dose increase, and adherence was good. There were no respiratory depressions and no deaths due to morphine. There were excess hospital admissions in the morphine arm but only three were attributable to morphine.

The absence of a difference in breathlessness measured during everyday activities, rather than at isotime or isoload, is consistent with clinical trials of morphine using similar measures, apart from one where participants were breathless at rest.[10] As breathlessness is intimately related to physical exertion, a person will exert to a so-called ceiling of breathlessness. However, if exercise tolerance improves, the amount of exertion required to hit that ceiling is increased. Hence, benefits seen under laboratory controlled conditions might not be replicated in daily life trials.[30] Physical activity was measured in both the MABEL and the BEAMS trial,[11,31] with the MABEL trial adding a larger dataset with actigraphy data. Although no statistically significant difference in average daily steps was found in either, some evidence of decreased sedentary time was seen in both, and MABEL showed increased time spent in moderate to vigorous activity (approximately 10 mins more per day than in the placebo group). Any reduction in sedentary behaviour is recommended for people living with chronic conditions by WHO.[32] Our point estimate data showed a mean reduction in sedentary behaviour of 20 min, and a 10 min increase in moderate to vigorous activity in the morphine arm compared with placebo. Although the reduction in sedentary behaviour is non-significant and imprecise, and irrespective of the accuracy of level of activity categorisation, this finding represents a potential area for future research.[33] Given the potential clinical importance for people living with debilitating chronic breathlessness, we propose that these data provide a rationale for further work with careful consideration regarding breathlessness measurement at isotime and isoload, and more accurate technology for a physical activity primary outcome.

Cough is a debilitating symptom affecting people with lung conditions.[34] With the largest dataset to date with a cough measure, and longest follow-up time, our findings add to the small literature regarding the potential use of morphine for chronic cough.[34,35]

The MORDYC trial showed a statistically significant improvement in the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test score in their trial of 20–30 mg daily modified release morphine.[36] We showed a marginal and non-statistically significant benefit only in quality-of-life measures (except ICECAP-SCM).

Adverse events were more common in the morphine arm but were mostly mild and resolved quickly, consistent with other published data showing resolution in the first week.[37] Most adverse events were gastrointestinal. There was no excess sedation or cognitive impairment

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and, consistent with previous findings,[38] no respiratory depression—all of which are key concerns for prescribers and patients. The absence of excess neurocognitive adverse events was reflected in lower study drug withdrawal and lower morphine-related harms than reported in similar trials.[39,31] Nevertheless, there was excess study drug withdrawal in the morphine arm (13 participants versus two participants). Only six of the 13 withdrawals cited drug toxicity, but a fuller understanding of reasons for withdrawal would be useful. Constipation remained an issue. In retrospect, the study laxative was suboptimal, and a softener–stimulant would further improve these figures. To our knowledge, this is the first study to report symptoms of physical withdrawal in relation to abrupt cessation of morphine after a maximum of 56 days. Some participants had moderate to severe symptoms, and therefore consideration should be given in practice to reducing the dose over a few days if a decision is made to stop morphine after weeks of treatment (or at least monitoring the individual for withdrawal symptoms). Also, we acknowledge that these findings need to be interpreted with caution due to the amount of missing data for this measure (about a third in the morphine arm, nearly a half in the placebo arm; appendix p 16).

This study was robustly conducted with low risk of bias and was adequately powered at 90%. Our mixed population increases generalisability. We had minimal attrition, and the dosing schedule started at a low dose, with the option for up-titration depending on tolerability. This conservative regimen, clinician training, and early monitoring and management of morphine-related harms was reflected in the better adherence and safety profile compared with previous trials of morphine for breathlessness. We found some evidence of benefit in relation to physical activity. The wrist-worn devices are known to overestimate steps and tend to misattribute a higher level of activity (eg, moderate for light, vigorous for moderate),[40] but this will be similar for both groups, and measures of sedentary behaviour will be more accurate than self-report.

Clinical trials in people with advanced disease and breathlessness are challenging and associated with high eligibility-to-consent ratios. Our ratio (four to one, with four people eligible for every one person who consented) is consistent with other morphine trials in people with COPD and breathlessness,[31,39] but better than in trials of people with heart failure and breathlessness.[41]

We had many secondary measures, and some findings might have occurred by chance. Therefore, any inferences should be considered exploratory only. However, although interpretation must be cautious, the observed findings are plausible and consistent with other evidence.[42,43] In addition, our measure of cough was limited and had no recognised minimal clinically important difference with which to assess relevance. Although the clinical descriptions support the attribution of serious adverse events, we accept that causality assessments could be biased. However, all (except one) were made whilst blinded. Two large cohorts of people with COPD[44] and interstitial lung disease[45] did not show any association between morphine dose equivalents of less than 30 mg/day and hospitalisation or death, which adds confidence to our assumption.

	28 days		56 days	
	Morphine (n=73)	Placebo (n=67)	Morphine (n=73)	Placebo (n=67)
Hospital inpatient stay, nights	0·6 (2·3)	0·1 (0·5)	0·9 (3·6)	0·3 (1·5)
Hospice inpatient stay, nights	0	0·1 (0·9)	0	0·1 (0·9)
Emergency department attendances	0 (0·1)	0 (0·2)	0 (0·2)	0 (0·2)
Outpatient attendances				
Specialist nurse	0·1 (0·3)	0·3 (1·2)	0·1 (0·3)	0·5 (1·5)
Hospital consultant or doctor	0·1 (0·2)	0·2 (0·4)	0·2 (0·5)	0·3 (0·6)
Physiotherapist	0·2 (1)	0·3 (1·2)	0·2 (1·1)	0·3 (1·3)
Occupational therapy	0 (0·1)	0 (0·3)	0 (0·1)	0 (0·3)
Other outpatient	0·1 (0·3)	0·1 (0·3)	0·1 (0·4)	0·4 (1)
Day hospice attendances	0	0 (0·3)	0	0·1 (0·4)
Phone calls				
Hospital consultant or doctor	0·1 (0·4)	0 (0·3)	0·2 (0·6)	0·1 (0·2)
Specialist nurse	0·1 (0·2)	0·4 (1·7)	0·3 (0·6)	0·7 (2·8)
Administrator or secretary	0 (0·1)	0 (0·1)	0·1 (0·3)	0·1 (0·4)
Hospice specialist nurse	0 (0·1)	0	0 (0·1)	0

Values presented as mean (SD) value per group per person.

Table 4: **Health-service use**

We did not include a measure of breathlessness at isotime or isoload, so improvements in exercise endurance can only be inferred from levels of physical activity. Lastly, although the eligibility criteria included people with other conditions, most participants had chronic lung disease. Females and people from minoritised ethnic communities were also under-represented.

Future studies could be designed with levels of physical activity as the primary outcome, and consideration given to including a measure of breathlessness taken at isotime or isoload using exercise short-forms tolerable to people with moderate to severe breathlessness (eg, 3-min incremental shuttle walk test, 1-min sit-to-stand).[46] The potential improvement in exercise endurance seen in laboratory testing might not translate to clinically important improvements in exercise endurance in people living with chronic breathlessness, but until such a trial is conducted, this remains an unanswered question.

In future research, we urgently need a better understanding of, and solutions for, the lack of representation from minoritised ethnic communities and women. The inclusion of fewer women in this study might have been, in part, due to men having a higher incidence of interstitial lung disease. A useful first step would be to collect ethnicity, sex, and gender data at screening, and to explore this issue with qualitative approaches. People from minoritised ethnic communities were under-represented in MABEL, but figures should be interpreted in the context of there being a lower prevalence of COPD in the UK population in those with Asian or Black ethnicity. Also, the average age of minoritised ethnic groups in the UK is younger than that of White groups, and COPD and interstitial lung disease are both diseases of older people.

Future work should also explore ways to include people with breathlessness due to other conditions. Studies might need to be specifically designed for people with cancer—very few were eligible in the MABEL study because of the requirement to be opioid naive.

There are important questions about symptom trial designs. Classic designs are single-symptom, single-endpoint, acknowledging that co-primary or composite endpoints can be problematic. However, this does not address the clinical reality that improved breathlessness can result in improved function which, in turn, induces more breathlessness. Future work should consider other options such as gatekeeping approaches.[47] Further, a single therapeutic approach in trials of a complex symptom makes little clinical sense when the accepted approach is an individualised management plan that draws on a multitude of components. In addition, many of our participants had multiple conditions, with mobility limitations not directly related to breathlessness (eg, arthritis). Our baseline participant characterisation did not have sufficient detail to allow for a more nuanced understanding of their breathlessness.

Lastly, funders should consider commissioning meta-analyses of secondary outcomes; this approach might be an efficient alternative to successive expensive and time-consuming trials with single primary outcomes.

In conclusion, we did not show a benefit of morphine for our primary outcome of breathlessness. However, secondary outcome findings taken together (some evidence of benefit [eg, cough, physical activity], some evidence of no difference [eg, morphine-related neurocognitive or respiratory harms], and newer insights into morphine-related harms [eg, morphine withdrawal, persistence of constipation despite resolution of nausea and vomiting]) alongside acceptable tolerability indicate that further research is needed to fully understand the role of morphine in people living with chronic breathlessness.

Contributors

Conceptualisation: MJJ, DCC, and MTF. Methodology: MJJ, DCC, MTF, CK, JN, JC, NC, SB, SH, MP, IJH, and PH. Validation: MJJ, CK, and ST. Formal analysis: MJJ, MTF, CK, ST, MA, and PH. Funding acquisition: MJJ, MTF, DCC, JN, JC, NC, SB, SH, MP, IJH, and PH. Access to raw data: ST, MA, and PH. Data curation: MJJ, BW, ST, PH, and MA. Verified the data: MJJ, CK, ST, PH and MA. Writing original draft: MJJ. Visualisation: MJJ, CK, ST, PH, MA, RAE, and DCC. Supervision: MJJ, MTF, JC, BW, JT, CK, JN, and PH. Project administration: MJJ, MTF, JC and BW. Software: CK, ST, PH, and MA. Decision to submit final manuscript: MJJ and MTF. All authors interpreted the data and contributed to the writing (review, critical input, and editing) of the Article.

Declaration of interests

MJJ reports grants from the National Institute for Health and Care Research (NIHR). MTF reports grants from NIHR; and is on the Pfizer Steering Committee and Ananda Advisory Board. IJH reports grants from the European Union, Marie Curie Cancer Care, and NIHR; is the scientific director of Cicely Saunders International and an NIHR Emeritus senior investigator; and is an Honorary Clinical Consultant in Palliative Medicine for hospitals under Kings College Hospital National Health Service Foundation Trust outside of the submitted work. DCC reports personal fees from Mayne Pharma International. JN is the Chair of the NIHR EME Funding Panel. PH reports institutional research funding from Lilly, Eisai, Novartis, Gilead, Sanofi, Roche, AstraZeneca, Novartis, DxCover, Abbvie, Merck, Sharp & Dohme, and SeaGen. SH is a trustee for Action for Pulmonary Fibrosis. RAE reports grants from NIHR, UK Research and Innovation, Wolfson Foundation, and Roche; consulting fees from AstraZeneca/Evidera for long COVID; speaker fees from Moderna; and is the chair of the European Respiratory Society Group 01·02 Pulmonary Rehabilitation and Chronic Care and the American Thoracic Society Pulmonary Rehabilitation Assembly. All other authors declare no competing interests.

Data sharing

Data supporting this work are available on reasonable request. All requests will be reviewed by relevant stakeholders, based on the principles of a controlled access approach. Requests to access anonymised data should be made to hhtuenquiries@hyms.ac.uk in the first instance.

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Morphine for chronic breathlessness: time to say goodbye

The effect of chronic breathlessness on the lives of patients and their loved ones is tremendous, regardless of the underlying cause.[1] Persistent breathlessness despite optimal treatment of the underlying disease is very common in chronic obstructive pulmonary disease (COPD), heart failure, cancer, and interstitial lung disease. Combined with the knowledge that the global burden of these diseases is still increasing,[2] it seems nearly impossible to overstate the need for effective breathlessness treatments.

Opioids for chronic breathlessness have been tested since the 1980s. A 2015 meta-analysis of 16 randomised controlled trials (RCTs; 271 patients) showed a positive effect of opioids on breathlessness,[3] and for a while it appeared that the biggest challenge was to convince health-care providers and patients to prescribe them for this indication. However, in recent years, the paradigm has shifted with the publication of several larger placebo-controlled RCTs investigating opioids for breathlessness, which did not show this same positive effect.[4] In a 2024 meta-analysis, Smallwood and colleagues made a distinction between daily life and laboratory exercise studies investigating opioids for breathlessness. They found that there was no effect of long-acting opioids on breathlessness in a daily life setting (10 RCTs, 788 patients), but did find a positive effect on breathlessness for trials investigating mainly single-dose, short-acting opioids during exercise testing (6 RCTs, 70 patients).[4]

The multicentre, parallel-group, double-blind, randomised, placebo-controlled MABEL trial by Miriam Johnson and colleagues,[5] published in *The Lancet Respiratory Medicine*, investigated the effectiveness of morphine in 143 patients with a cardiorespiratory condition and a modified Medical Research Council breathlessness score of 3 or greater. The primary endpoint was day 28 worst breathlessness measured by a numerical rating scale. In line with recent literature, there was no difference in breathlessness or quality of life between the study arms. This study is an important advance in our knowledge because it is adequately powered, well-designed, and has some interesting additional endpoints (such as coughing and physical activity). The MABEL trial had a treatment duration of 56 days, which is considerably longer than that of most trials investigating opioids for breathlessness, and chose a lower starting dose of morphine than is commonly used (5 mg twice daily), which is attractive because of the reduced risk of adverse effects. The dose could be increased to 10 mg twice daily. The primary endpoint was assessable for 66 (90%) participants in the morphine arm and 62 (93%) in the placebo arm at day 28, which is to be applauded in this vulnerable patient group. It is also commendable that the authors aimed to include a wide range of underlying conditions—however, the majority of participants had COPD (77 [55%]) or another lung disease (60 [43%], mainly interstitial lung disease [appendix p 6]).

The authors did describe two positive findings, which both merit further discussion. First, there was an adjusted mean difference of 9·51 (95% CI 0·54–18·48) more minutes per day spent in moderate to vigorous physical activity in the morphine arm, although this was not significant after multiple-measures correction. As the authors mention, this finding could explain why the worst breathlessness scores did not improve (as participants could have the same level of breathlessness but at a higher level of exertion). Even though the clinical importance of the effect size is unclear, there are potential positive effects of increased physical activity. However, before further research on opioids for physical activity is performed, it would be wise to consider whether patients will be motivated to use opioids for this indication because treatment with opioids is not something patients take lightly (due to concerns about addiction, side-effects, and association of opioids with end-of-life care).

Second, the authors describe a significant improvement in day 56 cough score of –1·41 points (95% CI –2·18 to –0·64) in favour of the morphine arm. This finding is not new. In fact, slow-release morphine is suggested because treatment in the British Thoracic Society's clinical statement on chronic cough.[6] Nevertheless, the finding is interesting as refractory chronic cough is common in cardiorespiratory conditions, known to decrease quality of life, and often lacks adequate treatment.[7] We do believe that these results should be interpreted with caution, especially since the patients included in the MABEL trial were not


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selected for coughing, and we do not know the effects of coughing on their quality of life.

In conclusion, the outcome of the MABEL trial contributes considerably to the evidence base against opioids for breathlessness. Combined with the lack of support for other medications such as mirtazapine and benzodiazepines,[8,9] we should probably focus much more on non-pharmacological treatments such as breathing and relaxation techniques, elements of cognitive behavioural therapy, a hand-held fan, or a crisis action plan.[10] Although the MABEL trial gave some indication for increased physical activity and decreased coughing, with the current status of the evidence, we suggest that the time has come to stop considering long-acting morphine for chronic breathlessness.

We declare no competing interests.

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