ORIGINAL ARTICLE

# Regular, sustained-release morphine for chronic breathlessness: a multicentre, double-blind, randomised, placebo-controlled trial

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## ABSTRACT

**Introduction** Morphine may decrease the intensity of chronic breathlessness but data from a large randomised controlled trial (RCT) are lacking. This first, large, parallel-group trial aimed to test the efficacy and safety of regular, low-dose, sustained-release (SR) morphine compared with placebo for chronic breathlessness.

**Methods** Multisite (14 inpatient and outpatient cardiorespiratory and palliative care services in Australia), parallel-arm, double-blind RCT. Adults with chronic breathlessness (modified Medical Research Council≥2) were randomised to 20 mg daily oral SR morphine and laxative (intervention) or placebo and placebo laxative (control) for 7 days. Both groups could take ≤6 doses of 2.5 mg, '*as needed*', immediate-release morphine (≤15 mg/24 hours) as required by the ethics review board. The primary endpoint was change from baseline in intensity of *breathlessness now* (0–100 mm visual analogue scale; two times per day diary) between groups. Secondary endpoints included: *worst*, *best* and *average breathlessness*; unpleasantness of *breathlessness now*, fatigue; quality of life; function; and harms.

**Results** Analysed by intention-to-treat, 284 participants were randomised to morphine (n=145) or placebo (n=139). There was no difference between arms for the primary endpoint (mean difference −0.15 mm (95% CI −4.59 to 4.29; p=0.95)), nor secondary endpoints. The placebo group used more doses of oral morphine solution during the treatment period (mean 8.7 vs 5.8 doses; p=0.001). The morphine group had more constipation and nausea/vomiting. There were no cases of respiratory depression nor obtundation.

**Conclusion** No differences were observed between arms for breathlessness, but the intervention arm used less rescue immediate-release morphine.

**Trial registration number** ACTRN12609000806268.

## Key messages

### What is the key question?

► Does regular, low-dose, sustained-release morphine provide a better reduction in *breathlessness now* than placebo in people with moderate-to-severe chronic breathlessness?

### What is the bottom line?

► There was no difference between arms in reduction of breathlessness now between the placebo and the intervention arm at 1 week.

### Why read on?

► This multisite study is larger than the cohorts assembled in the recent meta-analyses that have explored this question. Given the unrelieved symptom burden experienced by millions of people daily globally, it is imperative to find methods of reducing the symptomatic burden of chronic debilitating breathlessness.

## INTRODUCTION

Breathlessness at rest or on minimal exertion is prevalent in people with advanced disease and at the end of life.[1–3] Disabling breathlessness often persists despite optimal therapies for the underlying pathologies[4] and is associated with increased anxiety and depression,[5 6] impaired function,[6] poorer quality of life,[7] increased health service utilisation[8] and earlier death.[9] Chronic breathlessness causes considerable distress for patients, caregivers and healthcare providers.[10 11]

Until 2019, there had been no registered pharmacological treatment for the symptomatic reduction of chronic breathlessness.[5 12] Two meta-analyses of mostly small, crossover trials reported promising results for regular, low-dose, systemic opioids.[13–15] Most evidence pertains to patients with COPD and the use of oral sustained-release (SR) morphine.[15] A pooled analysis found that people with more severe breathlessness were more likely to benefit from morphine.[16]

Treatment with regular, low-dose, systemic opioids is recommended by several international consensus statements for palliating severe chronic breathlessness in advanced disease.[17–21] However, the optimal treatment of symptomatic chronic breathlessness needs further research, as studies were relatively small with limited standardised assessments of adverse events.[13 15 22] A particular concern for many clinicians is the potential risk that even low-dose opioids may cause respiratory depression, especially in people with severe illness. Associations between opioids and adverse outcomes

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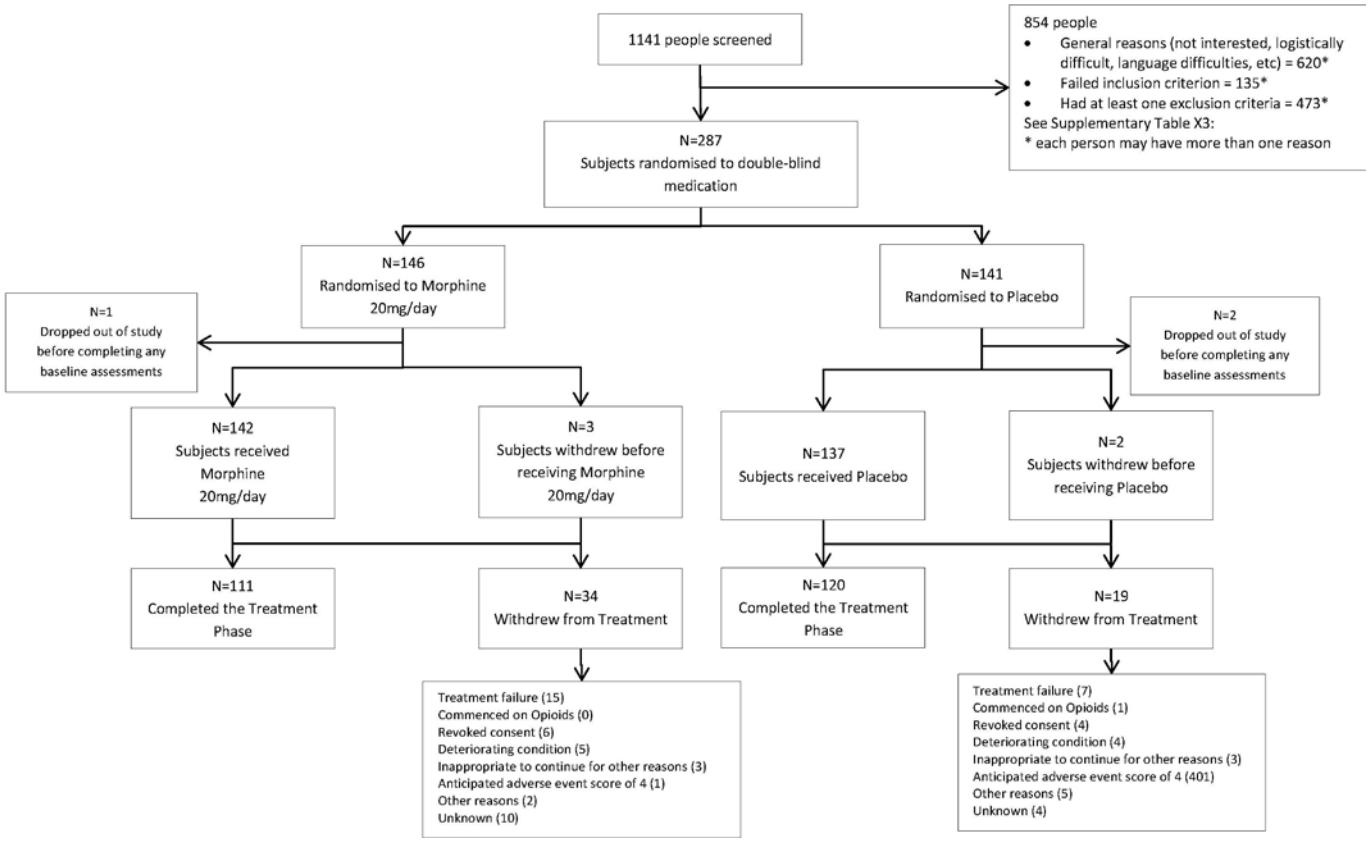


**Figure 1** CONSORT diagram.

have been conflicting in retrospective observational studies,[23–25] whereas serious adverse events have not been reported in the previous randomised controlled trials (RCTs).[15 23] A large, pragmatic, parallel-arm, RCT was needed to evaluate the clinical effectiveness and safety of regular, low-dose, systemic SR morphine, and to explore patient groups more likely to derive net benefit.

The primary aim of the present study was to determine the efficacy and safety of regular, low-dose, once daily, oral SR morphine compared with placebo for chronic breathlessness over 1 week in patients with severe disease.

## METHODS

### Study design and amendment

This was a phase III, multicentre, double-blind, randomised (1:1), parallel-arm trial of daily 20 mg oral SR morphine compared with placebo for 7 days. The trial was conducted and monitored in accordance with Good Clinical Practice (GCP).[26] An independent Data Safety Monitoring Committee reviewed all adverse event reports and conducted a prespecified, blinded interim analysis after 50% of planned completions to confirm baseline sample size estimates.

This trial initially included a third randomisation group (controlled-release oxycodone 5 mg PO three times a day) and required participants to have a modified Medical Research Council (mMRC) breathlessness score[27] of ≥3 to be included (figure 1). On 22 July 2014, due to insufficient recruitment (241 participants: oxycodone 74, morphine 86 and placebo 81) to meet the funded study timeframe for the primary comparison of morphine versus placebo, the trial was amended in consultation with the Trials Management Committee overseeing the study and approved by the Human Research Ethics Committee. Two changes were made: (1) mMRC eligibility criterion was changed from ≥3 to ≥2 and (2) the oxycodone randomisation group was deleted from the protocol and participants randomised to the morphine and placebo groups were retained in the present study. Trial registration was updated accordingly.

### Study population

Participants were recruited from 14 respiratory and palliative care services across Australia's National Palliative Care Clinical Studies Collaborative.

Inclusion criteria were: age≥18 years; chronic breathlessness defined as an mMRC[27] breathlessness score, initially ≥3 (February 2010 to July 2014) and then ≥2 at screening despite optimal management of underlying cause(s) of breathlessness as certified by the participant's treating physician; stable medications for breathlessness for the previous week except 'as needed' medications; the ability to speak and read English (fifth grade level); and expected survival of ≥2 months in the opinion of the treating physician.

Exclusion criteria were: treatment with ≥20 mg oral morphine equivalent per day in the 7 days before screening; Australia-modified Karnofsky Performance Status (AKPS) scale<40[28]; uncontrolled nausea, vomiting or gastrointestinal obstruction; calculated creatinine clearance<25 mL/min[29]; two or more hepatic enzymes≥3 times the upper limit of normal or international normalised ratio>1.2 when not on warfarin; unresolved respiratory or cardiac event in the previous week (excluding upper respiratory tract infections); resting respiratory rate≤8 $min^{-1}$; history of opioid-related respiratory failure; anaemia for which a blood transfusion was indicated for breathlessness; inability to give informed consent or complete diary entries; or being pregnant or breastfeeding.

### Randomisation and interventions

Participants were randomised (1:1) to a daily opaque capsule of 20 mg of oral morning SR morphine and two daily capsules of blinded laxative (docusate with sennosides), or similarly appearing placebo and placebo laxative capsules, for 7 days. Randomisation sequence was by blocks of four to ensure similar numbers of participants in each arm with stratification by site and dominant cause of breathlessness (COPD, cancer, end-stage cardiac failure, mixed or other). Additional open-label laxatives were available to all participants.

An SR morphine preparation was chosen because this delivers lower peaks and higher troughs[30] compared with immediate-release oral morphine solution. A fixed dose of 20 mg was chosen as it was safely used in a previous crossover RCT[14] and a longitudinal clinical trial with longer follow-up (mean 142 days (SD 190); median 29 days (range 2–660)).[31]

The Human Research Ethics Committee required that all participants could take up to six, '*as needed*', doses of immediate-release oral morphine solution 2.5 mg per dose per 24 hours.

### Assessments

Participants completed a diary on each of the seven treatment days documenting the intensity and unpleasantness of *breathlessness now* (morning and evening diary), and the *worst*, *best* and *average* breathlessness intensity over the previous 24 hours (evening diary). Breathlessness was self-reported on a 0–100 mm horizontal visual analogue scale (VAS) anchored between 0 ('none') and 100 ('worst possible' for intensity or 'the most unpleasant I have ever felt' for unpleasantness).

Assessments at baseline and end of treatment included measurements of participants' quality of life using the European Organization for Research and Treatment of Cancer—Quality of Life Questionnaire Core 15 PAL (EORTC-QLQ-C15 PAL; higher score reflects poorer quality of life)[32]; carers' quality of life using Carer Quality of Life Index—Cancer (CQOLC; higher scores reflecting better quality of life)[33]; and, at study end only, blinded participants' preferences to continue the assigned treatment group and global impression of change in overall health status from baseline.

Safety measures included oxygen saturation and end-tidal carbon dioxide ($CO_2$) measurement (Lifesense Monitor, Nonin Medical, Plymouth, Massachusetts, USA) at each contact, and Australia-modified Karnofsky Performance Scale (AKPS) weekly.[28]

Adverse events and vital status were assessed by the study staff at each contact. Assessment at baseline, during the mid-treatment week telephone call and during the weekly telephone calls, which occurred for 4 weeks after the end of treatment, used the National Institutes of Health Common Terminology Criteria for Adverse Events V.4.0.[34] Treatment emergent adverse events (TEAE) were defined as symptoms that appeared or worsened after baseline. The diary specifically sought symptoms that may be associated with morphine, including anxiety, appetite, concentration, confusion, constipation, nausea or vomiting, sleepiness and well-being, assessed using Likert scales. Use of '*as needed*' morphine was recorded by participants in the evening diary.

### Endpoints

The primary endpoint was change in intensity of *breathlessness now* ('How is your breathlessness right now?'; 100 mm VAS) from baseline to the average of the morning and evening scores of days 5–7.[35] This endpoint has been validated and was used in previous morphine RCTs.[14 15] An average of the last 3 days was chosen to ensure assessment at steady state of the treatment, and to minimise the influence of symptom fluctuations and missing data in this population with advanced disease.

Secondary endpoints were intensity of *worst*, *best and average* breathlessness in the previous 24 hours and unpleasantness of *breathlessness now*, participant health-related quality of life (EORTC-QLQ-C15 PAL overall and sub-domains), caregiver quality of life (CQOLC), participant treatment preference and use of 'as needed' morphine. Safety endpoints included changes in end-tidal $CO_2$, changes in functional status (AKPS), respiratory depression, confusion or obtundation and survival rate after first study drug.

### Sample size

A sample size of 235 participants with data provided 80% power to detect a clinically meaningful difference of 8.9 mm[36] between groups in the primary endpoint, assuming a SD of 22 mm on the 100 mm VAS based on a previous study,[14] and a significance level of 0.05 using a two-tailed test.

### Statistical analysis

All efficacy analyses were on an intention-to-treat (ITT) basis, which excluded three people randomised who did not complete any baseline or post-baseline data. The multiple imputation (MI) analyses were conducted using all ITT patients with at least one breathlessness result in the patient diary.

The primary and secondary endpoints were compared between groups using analysis of covariance, with change from baseline to the mean score of days 5–7 as the dependent variable. Independent variables were the allocated treatment group, stratification factors (study site, baseline dominant cause of breathlessness and an interaction term between these) and the baseline breathlessness score. Response was defined as an absolute difference of at least 8·9 mm in breathlessness from baseline to the mean of days 5–7.[16] Response was analysed using logistic regression with the same independent variables, with estimates expressed as OR. Missing values for the primary, secondary and subgroup analyses of breathlessness were imputed using Markov Chain Monte Carlo MI with 50 samples redrawn. Safety analyses included all participants who received at least one dose of study medication. Subgroup analyses were conducted in people with mMRC score 3 or 4 (the original study population).[16]

All estimates were presented with 95% CIs. P values were two-sided with the level of statistical significance set to 0.05. Secondary endpoints were exploratory and p values were not adjusted for multiple comparisons. All secondary analyses apart from the breathlessness analyses were conducted on the data as observed with no imputation for missing values. Analyses were performed with SAS V.9.4. This study is reported in compliance with the CONSORT statement for reporting RCTs.

### Ethics and registration

All subjects gave their informed written consent prior to participation. Part of the database was used for a published observational comparison of breathlessness intensity and severity.[35]

## RESULTS

Between February 2010 and July 2015, 1141 people were screened (online supplementary figure S1 and table S4) and 287 participants at 14 centres were randomised to either SR morphine 20 mg/day (n=146) or placebo (n=141; figure 1). Three participants did not provide any diary data and were excluded from the analysis. The 284 included participants had a mean age of 74.3 years (SD 9.33 years); 180 (63%) were male;

**Table 1** Baseline characteristics of participants in a multisite, placebo-controlled, parallel-arm study of 20 mg morphine daily for chronic breathlessness

| | | Intention-to-treat—whole population | |
|---|---|---|---|
| | | Morphine (n=145) | Placebo (n=139) |
| Age (years) | Mean (SD) | 74.0 (9.6) | 74.5 (9.1) |
| | Min, max | 44.8, 94.1 | 44.3, 89.4 |
| Gender, n (%) | Female | 52 (35.9%) | 52 (37.4%) |
| Performance status (AKPS) | Mean (SD) | 60.8 (11.5) | 61.5 (9.5) |
| | Min, max | 3, 90 | 40, 80 |
| BMI (kg/m$^2$) | Mean (SD) | 25.2 (7.6) | 25.9 (7.0) |
| | Min, max | 13.0, 66.1 | 12.3, 47.8 |
| mMRC *breathlessness now* score at baseline, n (%) | 1 | 18 (14.1%) | 12 (10.3%) |
| | 2 | 22 (17.2%) | 25 (21.6%) |
| | 3 | 33 (25.8%) | 33 (28.4%) |
| | 4 | 55 (43.0%) | 46 (39.7%) |
| Baseline mean (SD) breathlessness scores (0–100 mm visual analogue scale) | *Now* | 40.9 (22.0) | 42.9 (23.1) |
| | *Worst* | 58.5 (23.8) | 60.7 (24.9) |
| | *Best* | 28.3 (21.3) | 30.1 (20.5) |
| | *Average* | 41.2 (18.5) | 43.8 (20.6) |
| Charlson Comorbidity Index | Mean (SD) | 3.3 (2.46) | 3.2 (2.5) |
| | Min, max | 0, 12 | 1, 13 |
| Pulse oximetry $SpO_2$ (%) | Mean (SD) | 92.60 (4.17) | 92.96 (4.46) |
| | Min, max | 77.0, 99.0 | 72.0, 99.0 |
| End-tidal $CO_2$ (mm Hg) | Mean (SD) | 27.41 (8.29) | 25.53 (6.98) |
| | Min, max | 8.5, 53.1 | 9.9, 45.0 |
| Primary cause for breathlessness, n (%) | COPD | 82 (56.6%) | 82 (59.0%) |
| | Cancer | 26 (17.9%) | 22 (15.8%) |
| | Cardiac failure | 2 (1.4%) | 2 (1.4%) |
| | Mixed | 18 (12.4%) | 19 (13.7%) |
| | Other | 17 (11.7%) | 14 (10.1%) |
| Oxygen use | Yes, n (%) | 87 (60.0%) | 75 (54.0%) |
| Smoking status, n (%) | Never smoked | 24 (16.6%) | 26 (18.7%) |
| | Ex-smoker | 104 (71.7%) | 95 (68.3%) |
| | Current smoker | 17 (11.7%) | 16 (11.5%) |
| | Missing | 0 (0.00%) | 2 (1.4%) |

AKPS, Australia-modified Karnofsky Performance Status; BMI, body mass index; $CO_2$, carbon dioxide; mMRC, modified Medical Research Council.

164 (58%) had COPD; and 167 (59%) had an mMRC score of 3 or 4 at baseline (table 1). The proportion of participants completing the 7-day treatment period was lower for morphine (111/145; 77%) than placebo (120/139; 86%; figure 1).

### Efficacy endpoints

There was no clinically or statistically significant difference between treatment groups for the primary endpoint of *breathlessness now* (mean difference −0.15 mm; 95% CI −4.59 to 0.29; p=0.95; table 2). There were no clinically or statistically significant between-group differences for any of the secondary breathlessness efficacy endpoints (table 2).

### Rescue medication use

The mean number of doses of immediate-release oral morphine solution taken during the study was 55% higher in the placebo group (8.7; 95% CI 7.1 to 10.6) than in the morphine group (5.8; 95% CI 4.4 to 7.2); a mean 0.56 (95% CI 0.18 to 0.92; p=0.003) more doses per day of rescue morphine in the placebo group.

### Safety

The number of participants with one or more adverse event of special interest during the study was similar between treatment groups (table 3). TEAE grade 3–5 adverse were also similar between groups (morphine 72% vs placebo 83%; online supplementary table S1). More grade 3–5 adverse events occurred during the treatment week in the morphine than in the placebo group (52.7% vs 18.1%), which contributed to differential study withdrawal: (morphine 25.0% vs placebo 9.6%). A larger proportion of TEAE grade 3–5 did not resolve by the end of the follow-up period in the placebo (62.5%) than morphine group (33.3%; online supplementary table S1). Participants in the morphine group reported more constipation (56% vs 43%; p=0.037) and vomiting (37% vs 23%; p=0.012). They also reported a greater mean increase from baseline compared with placebo for constipation (13.47; 95% CI 5.31 to 21.62; p=0.001), nausea/vomiting (7.51; 95% CI 1.98 to 13.04; p=0.008) and fatigue (10.92; 95% CI 4.78 to 17.06; p<0.001) on the EORTC-QLQ-C15 PAL (table 2).

No participants had respiratory depression. There were no statistically nor clinically significant differences between morphine and placebo in mean change from baseline of respiratory rate (−1.13 bpm; 95% CI −2.43 to 0.18; p=0.089), end-tidal $CO_2$ (1.41 mm Hg; 95% CI −0.28 to 3.10; p=0.102) or pulse oximetry ($SpO_2$) (−1.01%; 95% CI −1.19% to 0.50%; p=0.43). Survival was similar 35 days after first study drug: morphine 84.0% and placebo 85.5% (online supplementary table S2).

### Subgroup analysis

Participants with a baseline mMRC of 3 or 4 (n=167; 59%; the original study population up until July 2014) had similar baseline characteristics (online supplementary table S3) and findings were similar to the whole study population. There were no clinically important differences for any of the primary or secondary endpoints. There was a trend of reduction by morphine in *worst breathlessness*, mean difference of −7.81 mm (95% CI −14.65 to −0.97) compared with placebo, and unpleasantness of *breathlessness now* (−6.15, 95% CI −12.13 to 0.18), but these findings were not seen for the other breathlessness endpoints (online supplementary table S3).

## DISCUSSION

In people with chronic breathlessness due to a range of conditions, 20 mg oral SR morphine showed no effect on intensity of *breathlessness now* or any of the secondary endpoints, including intensity of *worst*, *best* and *average* breathlessness, breathlessness unpleasantness, functional status, health-related quality of life in participants and caregivers or participant treatment preference in the intention-to-treat population.

The safety profile was consistent with previous RCTs of low-dose morphine.[13 22 23] SR morphine was well-tolerated with no

**Table 2** Treatment effects of sustained-release morphine 20 mg/day versus placebo from baseline to days 5–7 or end of treatment in the intention-to-treat population (n=284)

| | Morphine 20 mg/day (n=145) | Placebo (n=139) | Morphine versus placebo | |
|---|---|---|---|---|
| | Mean change from baseline (SE) | | Mean difference (95% CI) | P value |
| **Primary endpoint** | | | | |
| *Breathlessness now* (VAS) | −5.00 (2.13) | −4.86 (2.07) | −0.15 (−4.59 to 4.29) | 0.95 |
| **Secondary endpoints** | | | | |
| *Worst breathlessness*, 24 hours (VAS) | −10.51 (2.59) | −5.29 (2.61) | −5.23 (−10.77 to 0.31) | 0.064 |
| *Best breathlessness*, 24 hours (VAS) | −2.11 (2.14) | 0.80 (2.10) | −2.91 (−7.43 to 1.61) | 0.207 |
| *Average breathlessness*, 24 hours (VAS) | −4.49 (2.09) | −2.36 (2.06) | −2.13 (−6.64 to 2.38) | 0.355 |
| Breathlessness unpleasantness now (VAS) | −2.16 (2.21) | 0.10 (2.20) | −2.26 (−6.87 to 2.36) | 0.338 |
| Change in participant functional status (AKPS) | −1.15 (0.75) | −0.26 (0.75) | −0.89 (−2.44 to 0.66) | 0.260 |
| Participant health-related quality of life (EORTC-QLQ-C15 PAL) | 1.8 (2.2) | 1.5 (2.2) | 0.35 (−4.41 to 5.11) | 0.88 |
| Appetite loss (EORTC-QLQ-C15 PAL) | 3.0 (3.2) | 0.5 (3.2) | 2.46 (−4.22 to 9.14) | 0.47 |
| Constipation (EORTC-QLQ-C15 PAL) | 15.8 (3.8) | 2.3 (3.8) | 13.47 (5.31 to 21.62) | 0.001 |
| Dyspnoea (EORTC-QLQ-C15 PAL) | −7.0 (2.9) | −5.9 (2.8) | −1.08 (−7.14 to 4.98) | 0.73 |
| Emotional functioning (EORTC-QLQ-C15 PAL) | −0.8 (2.3) | 2.2 (2.3) | −3.08 (−7.97 to 1.81) | 0.215 |
| Fatigue (EORTC-QLQ-C15 PAL) | 6.1 (2.9) | −4.8 (2.9) | 10.92 (4.78 to 17.06) | <0.001 |
| Nausea/vomiting (EORTC-QLQ-C15 PAL) | 6.1 (2.6) | −1.4 (2.6) | 7.51 (1.98 to 13.04) | 0.008 |
| Pain (EORTC-QLQ-C15 PAL) | −1.1 (2.4) | 0.02 (2.4) | −1.12 (−6.28 to 4.05). | 0.67 |
| Physical functioning (EORTC-QLQ-C15 PAL) | −5.0 (2.3) | −0.6 (2.4) | −4.42 (−9.43 to 0.59) | 0.083 |
| Insomnia (EORTC-QLQ-C15 PAL) | −6.1 (3.5) | −8.4 (3.4) | 2.27 (−5.10 to 9.64) | 0.54 |
| Carers quality of life (CQOLC) | −1.4 (2.3) | −2.4 (3.2) | 0.94 (−7.70 to 9.58) | 0.82 |
| **Blinded treatment preference** | | | | |
| I have been less breathless during the past week | 64/132 (48.5%) | 66/134 (49.3%) | N/A | N/A |
| This medication would benefit me enough to be on it long term | 55/128 (43.0%) | 62/131 (47.3%) | N/A | N/A |

AKPS, Australia-modified Karnofsky Performance Status; CQOLC, Carer Quality of Life Index—Cancer; VAS, 100 mm visual analogue scale.

episodes of respiratory depression nor serious adverse events. Morphine was associated with increased rates of well-described opioid-related adverse effects of constipation, vomiting, nausea and fatigue. In this relatively large, opioid-naive population with severe illness, there were no hospital admissions for respiratory depression, confusion or obtundation. Observational data on associations between opioid treatment and adverse events have been conflicting.[24 37–39] Vozoris *et al* reported higher rates of hospitalisation and mortality in people with a COPD diagnosis in the community treated with opioids for any reason (with no data on why opioids were commenced nor the doses used).[24] In contrast, there were no clear associations for admission or death associated with low-dose opioids in people with severe oxygen-dependent COPD[22] or interstitial lung disease.[25] Further safety data from randomised and large prospective observational studies are needed to define the rates of more infrequent or longer-term events.

Rescue morphine use was lower in the morphine than the placebo group which could, at least partly, contribute to the lack of difference in endpoints between groups. However, the use was only a mean 0.56 doses (or 1.4 mg) daily higher in the placebo group which would be unlikely to mask any large treatment effect.

## Strengths

This is the first double-blind, randomised, parallel-group, multicentre, controlled trial of opioids for chronic breathlessness, and the largest study in this field to date. It was rigorously conducted, monitored in accordance with GCP standards and used validated endpoint measures relevant to the participant population.

## Limitations

A limitation was that the inclusion criteria were broadened from mMRC 3–4 to mMRC 2–4 two-thirds the way through the study to facilitate recruitment. Findings in the original target population with mMRC 3–4 was consistent with the main findings, with the addition of a trend for decreased *worst breathlessness* and unpleasantness of *breathlessness now* in the morphine arm. However, this trend was not seen across other breathlessness endpoints and might, in the light of the number of endpoints tested, represent a chance finding. This needs validation in further randomised trials. Of note, participant selection was by mMRC, which mainly assesses the functional disability and impact of breathlessness and not the intensity of the symptom itself (the primary endpoint).[17 27] mMRC is widely used for participant stratification in research and is strongly predictive of disease severity and clinical outcomes.[9 40] Complementing the mMRC were the baseline measures of chronic breathlessness, demonstrating a significant ongoing burden from the symptom.

A key limitation was the availability of 'as needed' immediate-release oral morphine to both groups, required by the ethics committee. Both arms will have differences reduced because both arms had exposure to morphine. The differences created are likely to be relatively small given that there were few doses taken in each arm on average. Future studies should be conducted without such rescue medication—an ethically defensible

**Table 3** Treatment emergent adverse events (TEAE) of special interest

| | | Safety population | |
|---|---|---|---|
| | | Morphine (n=142) | Placebo (n=137) |
| Subjects with at least one special interest TEAE | | 129 (90.8%) | 130 (94.9%) |
| Any respiratory disorder | | 61 (43.0%) | 71 (51.8%) |
| | Bronchospasm | 56 (39.4%)† | 65 (47.4%)† |
| | Wheezing | 3 (2.1%) | 4 (2.9%)† |
| Any gastrointestinal disorder | | 108 (76.1%) | 94 (68.6%) |
| | Abdominal pain or discomfort | 10 (7.0%) | 5 (3.6%) |
| | Constipation* | 79 (55.6%)† | 59 (43.1%)† |
| | Dry mouth | 36 (25.4%) | 40 (29.2%)† |
| | Nausea | 6 (4.2%) | 4 (2.9%) |
| | Vomiting** | 53 (37.3%) | 32 (23.4%)† |
| Any cardiac disorders | | 23 (16.2%) | 13 (9.5%) |
| | Arrhythmia | 22 (15.5%) | 13 (9.5%)† |
| | Bradycardia | 2 (1.4%) | 0 (0.0%) |
| | Tachycardia | 1 (0.7%) | 0 (0.0%) |
| Vascular disorders | | 20 (14.1%) | 23 (16.8%) |
| | Flushing | 7 (4.9%) | 10 (7.3%) |
| | Hypertension | 13 (9.2%) | 16 (11.7%)† |
| Any nervous system disorder | | 105 (73.9%) | 95 (69.3%) |
| | Dizziness | 37 (26.1%)† | 35 (25.5%)† |
| | Headache | 29 (20.4%)† | 27 (19.7%) |
| | Somnolence | 85 (59.9%)† | 70 (51.1%) |
| | Tremor | 26 (18.3%) | 20 (14.6%) |
| Any psychiatric disorder | | 56 (39.4%) | 53 (38.7%) |
| | Agitation | 37 (26.1%) | 38 (27.7%)† |
| | Delirium | 12 (8.5%)† | 10 (7.3%)† |
| | Mood altered | 21 (14.8%) | 21 (15.3%)† |
| Skin disorder | | 23 (16.2%) | 16 (11.7%) |
| | Rash | 0 (0.0%) | 1 (0.7%) |
| | Rash maculopapular | 0 (0.0%) | 1 (0.7%) |
| | Urticaria | 23 (16.2%) | 15 (10.9%) |

Data presented as frequency (percentage); *p=0.037 for difference between the groups; **p=0.012 for difference between groups.
†At least one participant experienced this TEAE with NCI-CTCAE severity grade 3, 4 or 5. The safety population included all participants who received at least one dose of study medication.
NCI-CTCAE, National Institutes of Health Common Terminology Criteria for Adverse Events.

approach. The present findings pertain to people without clinically significant hypercapnia. The study was for 1 week and trials with longer follow-up is needed. The largest prospective, open-label, dose-ranging study to date did not report evidence of any tachyphylaxis.[31]

## Implications for clinical care

This study did not confirm the reductions in breathlessness seen in previous smaller trials and meta-analyses.[15 25] For the clinician, the present results do not support the use of morphine for chronic breathlessness in people with advanced disease but who are mostly ambulatory, corresponding to the present study population. Given the potentially larger benefit of morphine in patients with worse symptoms,[16] the present findings need to be validated by further RCTs and especially in patients with more severe and disabling breathlessness. Except for increased rates of constipation and vomiting, which were expected and reversible effects of morphine, the treatment was well-tolerated.

## Implications for research

This study has identified a strong need for a large RCT to define the efficacy, optimal dose and target population of *worst breathlessness*, and to further evaluate the safety of SR morphine in people with severe chronic breathlessness.[41] Such a study should comprise standardised non-pharmacological supportive care and should not include any 'as needed' opioid treatment. Understanding the role of dose titration on chronic breathlessness in such a population is an important design feature of this study.

## Conclusion

In patients with optimally treated severe disease and chronic breathlessness (mMRC 2–4), 20 mg oral SR morphine daily was not observed to improve *breathlessness now* more than placebo, but the intervention arm used fewer doses of 'as needed' morphine. There were no serious adverse events.

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# Correction: *Regular, sustained-release morphine for chronic breathlessness: a multicentre, double-blind, randomised, placebo-controlled trial*

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Since the online publication of this article, the authors have noticed that one of the authors was listed incorrectly as Nikki McCaffery. The correct spelling is Nikki McCaffrey.



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