No excess harms from sustained release morphine compared with placebo; findings from a placebo-controlled randomised trial in chronic breathlessness.

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ABSTRACT

Objectives: We aimed to identify and evaluate i) treatment-emergent adverse events (TEAE [worse or new since baseline]) and the sub-group of severe TEAEs in a placebo-controlled seven-day randomised trial of regular, low-dose, sustained-release oral morphine for chronic breathlessness, and ii) clinical characteristics associated with TEAE.

Methods: Safety analysis of trial data. Adults with chronic breathlessness (modified Medical Research Council breathlessness score ≥2) due to heart or lung disease, or cancer, not on regular opioids were eligible. Symptoms associated with opioids (TEAE of special interest) were systematically sought using Common Terminology Criteria for Adverse Events (CTCAE) grading. Other harms could be reported at any time. The relationship between characteristics and presence of ≥1 TEAE of special interest was explored using univariable logistic regression analyses.

Results: 1449/5624 (26%) AEs from 279 participants were TEAE of which 150/1449 (10%) were severe (CTCAE grades 3 -5). 1086/5624 (75%) were events of special interest of which 41/1086 (4%) were severe. Compared with placebo, morphine was not associated with more TEAE or severe TEAE of special interest (TEAE: odds ratio 0.53, 95% CI 0.21 to 1.38, p=0.20; severe TEAE: odds ratio 0.96, 95% CI 0.27 to 3.41, p=0.95) nor with CTCAE severity grade (X^2=4.39, p=0.50). Amongst the 26/150 (17%) with severe TEAEs, study withdrawal was more common in the morphine arm (18/26 [69%] morphine arm; 8/26 [30%] placebo arm). None of the severe TEAEs was a respiratory harm.

Conclusions: Severe morphine-associated toxicity was uncommon and not associated with study arm. Clinical consequences were minor and self-limiting.

INTRODUCTION

Morphine has been used for thousands of years as an analgesic and the profile of harms when used for pain, ranging from mild and self-limiting to serious and life-threatening, are well documented. The most common harms of all opioid medications are constipation almost universally and nausea, mainly as the medication is initiated. Both side-effects can be successfully managed for most people. Respiratory depression is the most feared consequence of opioids. Clinically, from first principles, best practice is that opioids are prescribed at the lowest dose possible aiming for adequate analgesia which allows improvement in function and quality of life.

The evidence base is growing for the use of regular, low-dose (<30mg/day), sustained-release oral morphine [1] for people with chronic breathlessness (disabling breathlessness despite optimum treatment of the underlying cause),[2] with the most robust data being for patients with chronic obstructive pulmonary disease with a modified Medical Research Council (mMRC) breathlessness grade of 3 or 4.[3] This is reflected in the guidance issued by leading clinical bodies around the world,[4-8] and the recent extension of licence to include the indication of chronic breathlessness for Kapanol®, a sustained release morphine preparation, by the Therapeutic Goods Administration of Australia.[9]

As the regular use of low-dose oral morphine may be considered for people with advanced cardio-respiratory disease and chronic breathlessness, most of whom already suffer from poor respiratory reserve, respiratory depression remains a major fear. It is a concern for clinicians prescribing morphine for the clinical indication of chronic breathlessness.[10] Patient resistance is also cited as a reason for non-prescription by professionals although evidence for this is largely lacking.[11] Patients' opioid-fears are well known, particularly amongst people with cancer, and concerns about addiction, confusion and sedation are common.[12] However, patient experience of taking sustained-release morphine for chronic breathlessness in supported practice appears to be good.[13] One study found some patients' concerns seemed to be prompted by the clinician.[14] Adding to this is the consistent and persistent medication authority warnings and contraindications in people with cardio-respiratory disease, well known by clinicians and spelled out in patient information sheets. Getting the balance right is important; to avoid overuse in the population while allowing needed and appropriate treatment of intractable symptoms in people with advanced life-limiting illness.

Accurate information on risks and management of morphine-induced symptoms is important in patients' and clinicians' choices as to whether using the medication could provide net benefits. Data from randomised controlled trials (RCTs) in chronic breathlessness are limited. A key role for RCTs is to quantify directly-attributable harms in excess of those that would have been experienced without the intervention − treatment emergent adverse events (TEAE).[15] TEAEs are defined as symptoms that appear or worsen after baseline.[15] As the patient population in which opioids might be considered for chronic breathlessness have advanced disease, often with comorbidities and reduced performance status, such placebo-controlled safety data are crucial.

The primary aim of this study was to identify TEAE data collected in a placebo-controlled phase III RCT of sustained-release (SR) morphine for chronic breathlessness and to evaluate if these are more common or more severe in the morphine compared with the placebo arm.

The secondary aim was to identify clinical characteristics associated with TEAE (including allocation to morphine arm) in this study population. Effectiveness data and descriptive TEAE are reported elsewhere.[16]

METHODS

Participants and safety data collection

This was a parallel group, multi-centre, double-blind, placebo-controlled, fixed-dose randomised (1:1) seven day trial of 20 mg once daily oral SR morphine and laxative, and matched blinded study drug and laxative (ACTRN126000806268). Immediate-release morphine for breathlessness could also be taken "as needed" in 4-hourly 2.5mg doses in both arms. Participants were adults, not on regular opioids, with a modified Medical Research Council (mMRC) breathlessness score ≥2 at screening despite optimal treatment of their medical condition causing breathlessness [2] (heart or lung disease, or cancer) with no contraindications to morphine. People with moderate renal impairment or worse (calculated GFR ≤25mls/min), poor performance status (≤30 on the Australia-modified Karnofsky Performance Status [AKPS]),[17] or increased liver function tests (enzymes 3 x upper limit of normal) were excluded.

Harms were sought prospectively and systematically during the 7 days' treatment and for the four following weeks. Assessment was conducted by the study nurse at baseline, during the treatment week and then weekly *post*-treatment *via* telephone calls for four weeks.

Ethics approval was obtained by all participating sites and the trial was registered (ACTRN126000806268) before first enrolment at any site. All participants provided written, informed consent. The trial was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement.[18]

Outcomes

A daily patient diary specifically sought symptoms that may be associated with opioids (anxiety, appetite, concentration, confusion, constipation, nausea or vomiting, sleepiness and reduced well-being) and the National Institutes of Health NCI CTCAE version 4.0 Likert grades adverse events were used for *ad hoc* reporting.[19] Any adverse event recorded was counted as a TEAE if it appeared or worsened after baseline (noting high baseline symptom burdens for all symptoms of interest). A TEAE with a CTCAE grade of ≥3, or otherwise reported as a Serious Adverse Event as part of trial pharmacovigilance reporting, was categorised as a severe TEAE.

The potentially opioid-related symptoms in the patient diary were identified *a priori* from the literature and collected in the trial as TEAEs of *special interest* together with any other harms reported. Of note, respiratory harms were assessed using pulse oximetry, end-tidal CO2, respiratory rate and SAE clinical reports. The outcome of the TEAE was noted (recovered/resolved; recovering/resolving; not recovered/resolved; recovered/resolved with sequelae) and whether or not it was accompanied by study participant withdrawal.

Statistical analyses

Outcomes were compared between study groups (morphine or placebo) using chi squared and t-tests as appropriate.

In order to explore potential clinical predictors of TEAEs of special interest, a dependent variable was created (to indicate whether a participant experienced at least one TEAE of *special interest* during the reporting period) and associations for biologically plausible explanatory variables at baseline were explored using univariable logistic regression. Explanatory variables included: study arm, sex, age: end-tidal carbon dioxide (EtCO2) levels; AKPS,[17] body mass index (BMI), Charlson Comorbidity Index (CCI),[20] mMRC,[21] and renal function (creatinine clearance). Explanatory variables with evidence of statistically significant association with the dependent variable (assessed at $p<0.10$) were explored in a multiple logistic regression model in this exploratory study. This analysis was also repeated with at least one *severe* TEAE of special interest as the dependent variable.

RESULTS

Fourteen study sites randomised 284 participants to morphine (n=145) or placebo (n=139) between 2010 and 2015. The 284 patients had a mean age of 74.3 years (SD 9.3); 180 (63%) were male; 164 (58%) had COPD; and 167 (59%) had a baseline mMRC score of 3 or 4. The median AKPS was 60 (interquartile range [IQR] 50 to 70) and the median CCI Score was 3 (IQR 1 to 4). Baseline characteristics were comparable (see Table 1). Five participants (three in the morphine group and two in the placebo group) did not receive study medication and were not included in this safety dataset resulting in a population of 279 participants (142 in the morphine group and 137 in the placebo group).

Table 1: Characteristics of participants in a multi-site, placebo-controlled, parallel arm, fixed dose study of 20mg sustained 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)
Sex; n (%)	Female	52 (35.9%)	52 (37.4%)
Performance status (AKPS); mean (SD)		60.8 (11.5)	61.5 (9.5)
BMI (kg/m^2); mean (SD)		25.2 (7.6)	25.9 (7.0)
Clinician-rated mMRC *breathlessness now* score at eligibility n (%)	2	13 (9%)	12 (8.6%)
	3	73 (50.3%)	69 (49.6%)
	4	59 (40.7%)	58 (41.7%)
Baseline mean (SD) breathlessness scores (0-100mm visual analogue scale (VAS)); mean (SD)	*now*	40.9 (22.0)	42.9 (23.1)
	worst	58.5 (23.8)	60.7 (24.9)
	average	41.2 (18.5)	43.8 (20.6)
Charlson Co-morbidity Index; median (range)		3.00 (0.0, 12.0)	2.00 (1.0, 13.0)
Pulse oximetry SpO_2 (%); mean (SD)		92.60 (4.17)	92.96 (4.46)
End-tidal CO_2 (mmHg); mean (SD)		27.41 (8.29)	25.53 (6.98)
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; n (%)	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%)

Abbreviations: AKPS – Australia-modified Karnofsky Performance Status; BMI body mass index; CO_2 carbon dioxide; COPD – chronic obstructive pulmonary disease; mMRC modified Medical Research Council breathlessness score.

Morphine dose by arm

Table 2 presents summaries of daily, total and average morphine use (mgs) for the morphine and placebo groups, and overall. This accounts for the active treatment, of 20mg a day when taken, for the morphine group plus "as needed" 2.5mg doses of immediate-release morphine for both groups. On average, per day, patients in the morphine group took 22.5mg (SD 3.3) of morphine, whilst the placebo group took 3.6mg (SD 3.8) which was all “as needed”. Figure 1 shows the change in average dose used by study arm over the 7 days. The average daily dose is lower when missing data are assumed to be 0mg (morphine group: mean 16.6, SD 7.9; placebo group: mean 2.9, SD 3.3).

Table 2. Morphine use by study arm

Morphine use, mg	Morphine (n=145)		Placebo (n=139)		Total (n=284)	
	excludes missing data	assumes missing data are 0mg	excludes missing data	assumes missing data are 0mg	excludes missing data	assumes missing data are 0mg
Day 1	22.0 (3.3)	18.8 (8.3)	2.7 (4.1)	2.4 (3.9)	12.3 (10.3)	10.8 (10.5)
	20.0 (20.0, 40.0)	20.0 (0.0, 40.0)	0.0 (0.0, 30.0)	0.0 (0.0, 30.0)	20.0 (0.0, 40.0)	7.5 (0.0, 40.0)
Day 2	22.5 (3.8)	19.2 (8.7)	3.4 (3.9)	2.9 (3.8)	13.2 (10.3)	11.2 (10.6)
	20.0 (20.0, 40.0)	20.0 (0.0, 40.0)	2.5 (0.0, 15.0)	0.0 (0.0, 15.0)	20.0 (0.0, 40.0)	7.5 (0.0, 40.0)
Day 3	22.8 (3.9)	18.2 (9.8)	3.6 (3.9)	3.1 (3.9)	13.1 (10.4)	10.8 (10.6)
	20.0 (20.0, 40.0)	20.0 (0.0, 40.0)	2.5 (0.0, 15.0)	2.5 (0.0, 15.0)	12.5 (0.0, 40.0)	7.5 (0.0, 40.0)
Day 4	22.7 (4.1)	17.5 (10.2)	4.1 (4.4)	3.5 (4.3)	13.2 (10.2)	10.7 (10.6)
	20.0 (20.0, 40.0)	20.0 (0.0, 40.0)	2.5 (0.0, 17.5)	2.5 (0.0, 17.5)	15.0 (0.0, 40.0)	7.5 (0.0, 40.0)
Day 5	22.8 (4.1)	17.1 (10.5)	4.1 (4.6)	3.4 (4.5)	13.2 (10.3)	10.4 (10.6)
	20.0 (20.0, 40.0)	20.0 (0.0, 40.0)	2.5 (0.0, 22.5)	2.5 (0.0, 22.5)	15.0 (0.0, 40.0)	5.0 (0.0, 40.0)
Day 6	22.7 (4.0)	16.8 (10.6)	4.2 (4.7)	3.6 (4.6)	12.9 (10.3)	10.3 (10.5)
	20.0 (20.0, 42.5)	20.0 (0.0, 42.5)	2.5 (0.0, 25.0)	2.5 (0.0, 25.0)	12.5 (0.0, 42.5)	5.0 (0.0, 42.5)
Day 7	22.2 (2.8)	8.6 (11.0)	3.7 (4.4)	1.7 (3.5)	12.3 (10.0)	5.2 (8.9)
	20.0 (20.0, 30.0)	0.0 (0.0, 30.0)	2.5 (0.0, 20.0)	0.0 (0.0, 20.0)	11.3 (0.0, 30.0)	0.0 (0.0, 30.0)
Total	116.2 (55.2)	116.2 (55.2)	20.6 (23.3)	20.6 (23.3)	69.4 (64.1)	69.4 (64.1)
	130.0 (0.0, 227.5)	130.0 (0.0, 227.5)	12.5 (0.0, 107.5)	12.5 (0.0, 107.5)	46.3 (0.0, 227.5)	46.3 (0.0, 227.5)
Average per day	22.5 (3.3)	16.6 (7.9)	3.6 (3.8)	2.9 (3.3)	13.0 (10.1)	9.9 (9.2)
	21.3 (20.0, 37.5)	18.6 (0.0, 32.5)	2.9 (0.0, 16.7)	1.8 (0.0, 15.4)	16.7 (0.0, 37.5)	6.6 (0.0, 32.5)

Figures are mean (SD), median (maximum, maximum): For some participants, their morphine use data were missing for a particular day. For each treatment group, the first column excludes missing data and the second columns assumes missing data are zero

Treatment Emergent Adverse Events (worse or new since baseline) by mean morphine use

Overall, 5624 adverse events were recorded, of which 1449 (26%) were TEAEs; 767 TEAEs for 138 (97%) of the participants in the morphine groups, and 683 TEAEs for 132 (96%) of the participants in the placebo group. Ten percent of the TEAEs (n=150) were severe; CTCAE grade 3-5 (Table 3) (69 for 38 participants in the morphine group, and 81 for 39 participants in the placebo group). A chi-squared test indicates there is no evidence of an association between treatment group and CTCAE grade (X^2=4.39, p=0.50).

Table 3. CTCAE grades for TEAEs by study group, n (%).

CTCAE grade	TEAEs in Morphine Group (n=767)	TEAEs in Placebo Group (n=683)	Total (n=1449)
1	468 (61.0)	398 (58.4)	866 (59.8)
2	227 (29.6)	201 (29.5)	428 (29.5)
3	54 (7.0)	59 (8.7)	113 (7.8)
4	8 (1.0)	14 (2.1)	22 (1.5)
5	7 (0.9)	8 (1.2)	15 (1.0)
Ungraded	3 (0.4)	2 (0.3)	5 (0.4)

CTCAE, Common Terminology Criteria for Adverse Events; TEAE, Treatment Emergent Adverse Event. At least one TEAE reported for 139 participants in the morphine group and 132 in the placebo group.

Individual symptom/respiratory harm details are presented elsewhere.[16] Participants in the morphine group reported more constipation (56% vs 43%; p=0.037) and vomiting (37% vs 23%; p=0.012). There was no statistically or clinically significant differences in mean change from baseline any measurement of respiratory harm in either arm.[16]

Twenty-six severe TEAEs (17%) resulted in study withdrawal (18 [69%] from the morphine arm, and 8 [30%] from the placebo arm). The reported outcomes of the severe TEAEs are reported in Table 4. Of note, none of these related to respiratory harms.

Table 4. Severe TEAE outcomes

Outcome	Withdrew from study, n (%)			Remained in study, n (%)		
	Placebo (n=8)	Morphine (n=17)	Total (n=25)	Placebo (n=73)	Morphine (n=52)	Total (n=125)
Resolved	1 (12.5)	1 (5.9)	2 (8.0)	7 (9.6)	3 (5.8)	10 (8.0)
Resolving	1 (12.5)	4 (23.5)	5 (20.0)	18 (24.7)	15 (28.9)	33 (26.4)
Unresolved	5 (62.5)	6 (35.3)	11 (44.0)	8 (11.0)	7 (13.5)	15 (12.0)
Resolved with sequelae	0 (0.0)	1 (5.9)	1 (4.0)	1 (1.4)	3 (5.8)	4 (3.2)
Not reported	1 (12.5)	5 (29.4)	6 (24.0)	39 (53.4)	24 (46.2)	63 (50.4)

Treatment Emergent Adverse Events of special interest

Among the 1449 TEAEs, 1086 (75%) were events of special interest (morphine 583/767 [76%]; placebo 503/682 [74%]). Two hundred and fifty nine participants (93%) had at least one TEAE of special interest (129 (91%) in the morphine group, and 130 (95%) in the placebo group). Forty-one (4%) of the special interest TEAEs were graded 3-5 (16 events for 11 participants in the morphine group, and 25 events for 16 participants in the placebo group).

Predictors of TEAE of special interest

Table 5 presents the results of the logistic regression analyses for special interest TEAEs (all and severe).

Among the evaluated predictors, only sex was related with the risk of severe TEAEs; women were more likely to have a severe TEAE of special interest (OR 4.27, 95% CI 1.08 to 16.91, p=0.04). Treatment arm was not related (OR 0.96, 95% CI 0.27 to 3.41, p=0.95.

In view of the lack of associated explanatory variables, multiple regression was not performed in this exploratory study.

Table 5. Univariable analyses to predict likelihood of developing a (severe) TEAE of special interest with baseline factors

	TEAE of special interest				**Severe TEAE of special interest**			
Variable (reference group for categorical data)	**Odds Ratio**	**Standard error**	**95% CI**	**P value**	**Odds Ratio**	**Standard error**	**95% CI**	**P value**
Sex (male) n=279	2.43	1.40	0.79 to 7.49	0.12	4.27	3.00	1.08 to 16.91	**0.04**
Age, years n=276	1.02	0.02	0.98 to 1.07	0.34	1.07	0.05	0.98 to 1.17	0.12
Treatment group (placebo) n=279	0.53	0.26	0.21 to 1.38	0.20	0.96	0.62	0.27 to 3.41	0.95
EtCO2 n=253	0.98	0.03	0.92 to 1.04	0.49	1.05	0.05	0.97 to 1.15	0.23
AKPS n=279	1.02	0.02	0.98 to 1.07	0.26	0.97	0.03	0.92 to 1.03	0.33
CCI n=276	1.05	0.11	0.86 to 1.28	0.64	0.96	0.13	0.74 to 1.26	0.80
mMRC[a]								
Grade 2	1.59	2.27	0.10 to	0.75	*			
Grade 3[a]	0.34	0.37	26.36	0.33	*			
Grade 4[a] n=243	0.40	0.43	0.04 to 2.95 0.05 to 3.34	0.40	*			
BMI n=266	1.08	0.05	0.99 to 1.17	**0.09**	1.03	0.04	0.95 to 1.11	0.46

Creatinine Clearance n=279	1.00	0.01	0.99 to 1.01	0.98	0.98	0.01	0.95 to 1.01	0.15

* insufficient data for analysis; EtCO2 end tidal carbon dioxide; AKPS Australian-modified Karnofsky Performace Status; CCI Charlson Comorbidity Index; mMRC modified Medical Research Council breathlessness scale; BMI body mass index.

[a] reference group mMRC=1

DISCUSSION

People with chronic breathlessness due to advanced cardio-respiratory disease or cancer experience a large number of symptoms and have an underlying high risk of deterioration. In this study, 279 participants reported 5624 adverse events but only a quarter of these developed *de novo* or worsened from baseline and thus are of relevance in this placebo-controlled trial of oral morphine. Fewer than one in twenty experienced a severe event of special interest and none was a respiratory harm. Of particular note, morphine was not related to either TEAE or severe TEAE in this study population. There were no baseline clinico-demographic predictors of TEAEs or severe TEAE other than the indication that being a woman marginally increased the risk. Notably, renal function, comorbidity and performance status were not associated despite significant impairment of these variables in many of the trial population.

Interestingly, even though no relationship between severe TEAE and morphine was demonstrated, for those where a severe TEAE led to trial withdrawal, this was more likely in the morphine arm. This may indicate that despite rigorous, objective measures of harms, there may be a qualitative aspect which is not captured in these data and which contributes to withdrawal.

This study highlights the crucial importance of placebo-controlled trials for interventions where the evidence base for net-benefit is still developing and in patient populations with advanced disease with such high baseline burden of symptom. Further, there is evidence of investigator bias in adverse event attribution in favour of disease progression rather than the intervention that has been introduced.[22] This effectiveness study had inclusive eligibility criteria reflecting the patient population for whom morphine is already being prescribed in much of the world to reduce the symptomatic burden of chronic breathlessness.[23, 24]

There were no instances of severe respiratory harms in this phase III study over seven days, where morphine was given to patients who were not on regular opioid treatment.[11] The lack of respiratory harms is consistent with a recent systematic review and meta-analysis of 1064 patients from 67 studies with a range of study designs.[25] In one subgroup analysis there was a statistically significant increase in partial pressure of carbon dioxide and an insignificant reduction of partial pressure of oxygen and oxygen saturation, but the changes were clinically irrelevant. Only four participants had (non-serious) respiratory depression (variably defined, or not at all) and only one required temporary ventilator assistance for a reduced respiratory rate. This occurred after administration of 4 mg nebulized morphine for

breakthrough breathlessness in a patient taking 30 mg oral slow-release morphine *per* day and 10 mg oral immediate release morphine when required for cancer-related pain.[26]

Limitations

These are short-term data of treatment over seven days, with follow up for the 4 weeks *post*-treatment. However, they explore harms to patients at the time they are at most risk, that is, at dose initiation. Once at steady state, unless the dose increases or some other factor such as deterioration in renal function occurs, then one would not expect further TEAEs. Longer-term open label observational data (median 142 days, range 1 – 662 days) have been reported previously and are consistent with these findings,[27] however, in view of the benefit of placebo-controlled measures, ongoing trials have longer follow up (BEAMS, NCT02720822;[28] MORDYC, NCT02429050[29]). This current study is unable to inform regarding longer-term problems with abuse or harms in relation to hormone or immune status, although the formulation used (sustained release morphine sulphate) is one least likely to be associated with abuse[30] or overdose related deaths.[31]

The allowed use of immediate release morphine for "as needed" use in both arms may have led to an underestimation of a toxicity difference between the two arms. However, the average 24 hour dose in the placebo group was less than 5mg, which given morphine's oral bioavailability (10 to 50%) is unlikely to be responsible for significant adverse events.

Even though none of the variables showed a statistically significant signal at univariable analysis, we could have built a model using variables with a plausible explanation for association. However, we deemed in this exploratory study we should be cautious about the risks of over-interpretation.

Strengths

This study includes more participants than those from all included studies the most recent systematic review put together (n=279 compared with n = 198).[1] This study was prospective, multi-site, blinded, placebo-controlled, had broad (effectiveness) eligibility criteria and used standard measures so the natural history of the underlying disease(s) could be defined and causality attributed. There was frequent contact with participants and TEAE were systematically sought.

Clinical implications

Clinicians can treat chronically breathless opioid-naïve patients confidently with this starting dose of regular, low-dose, oral sustained release morphine in the context of careful patient selection and ongoing appropriate monitoring. The absence of an identified sub-group at greater risk of harms gives further confidence in the careful use of this drug in this formulation. However, it is notable that twice as many participants with severe TEAE in the morphine arm withdrew from the study than in the placebo arm, although the absolute numbers are small. Although we found no association by study arm, it is good practice to assess and manage morphine-related harms such as constipation rigorously and expertly from morphine initiation. Failure to do so may reduce net-benefit even in those who continue on morphine because they are experiencing symptomatic improvement in their chronic breathlessness.[32]

Research implications

Conservative lower limits of renal function were used as an eligibility criterion but no TEAE harms relating to renal dysfunction were seen. Further work is needed to understand the safe lowest level of glomerular filtration rate in order to avoid limiting this therapy unnecessarily to people who may benefit. We do not know if patients with an initial response would gain further *net*-benefit by upward titration. A blinded dose titration placebo-controlled randomised trial is currently recruiting with a starting dose of 8mg/24hours sustained release morphine.[28]

CONCLUSION

Low-dose sustained release oral morphine appeared to be safe in this placebo-controlled trial. Only one quarter of adverse events were treatment emergent (developed *de novo* or worsened from baseline). Severe events of special interest were uncommon and clinical consequences were minor and self-limiting. Of note, none was a respiratory harm. Morphine was not related to either TEAE or severe TEAE in this study population. Although there was no excess TEAEs ≥2, more participants withdrew from study drug in the intervention arm highlighting the importance of meticulous prospective management of side-effects.

Author contributions

Concept and design: MJJ, DCC. Protocol authors; MJJ, DCC, CF, IS. Data analysis: CF, IS. Data interpretation: All; revisions of manuscript for intellectual content and approved final version: All.

Declaration of competing interest.

DCC has received an unrestricted research grant from Mundipharma, is an unpaid member of an advisory board for Helsinn Pharmaceuticals and has consulted Mayne Pharma and received intellectual property payments from them. MJJ has received consulting payments from Mayne Pharma. No other authors have any conflicting interests with the content of this manuscript.

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Data management and sharing.

Requests to access data can be made to Prof. David Currow (david.currow@uts.edu.au). Requests will be considered on a case-by-case basis and managed according to the Palliative Care Clinical Studies Collaboration processes and procedures.

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Figure 1. Mean daily morphine dose over time by study arm