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TITLE: Effects of low dose morphine on perceived sleep quality in patients with refractory breathlessness: A hypothesis generating study

AUTHORS: Rodrigo T. Martins MD^{1,2}, David C. Currow B Med, MPH, PhD, FRACP³, Amy P. Abernethy MD, PhD⁴, Miriam J. Johnson MBChB (Hons), MD, FRCP, MRCP⁵, Barbara Toson BStatEc¹, Danny J. Eckert PhD^{1,2}

INSTITUTIONS:

1. Neuroscience Research Australia (NeuRA), Randwick, Sydney, NSW, AUSTRALIA.
2. School of Medical Sciences, University of New South Wales, Sydney, NSW, AUSTRALIA.
3. *Discipline, Palliative and Supportive Services, Flinders University, Bedford Park, South Australia, AUSTRALIA. **Institution in which the work was performed.*
4. Department of Medicine, Division on Medical Oncology and the Center for Learning Health Care, Duke Clinical Research Institute, Duke University, Durham NC, USA.
5. Hull York Medical School, The University of Hull, Hull, UK.

CORRESPONDENCE: Danny J. Eckert, PhD (d.eckert@neura.edu.au)

ADDRESS: Neuroscience Research Australia (NeuRA)
PO Box 1165, Randwick, NSW, AUSTRALIA 2031.

TELEPHONE: +61 (2) 9399 1814

FAXMILE: +61 (2) 9399 1027

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SUMMARY AT A GLANCE : This study compared perceived sleep disruption due to breathlessness and sleep quality during four days of regular low dose (20mg sustained release) oral morphine versus placebo in elderly participants with refractory breathlessness. This is the first study to raise the possibility that low dose morphine to reduce breathlessness may also improve sleep quality and vice versa.

ABSTRACT

Background and Objectives: The management of chronic refractory breathlessness is one of the indications for regular low dose ($\leq 30\text{mg}/24\text{hrs}$) oral sustained release morphine. Morphine may disrupt sleep in some conditions and improve sleep quality in others. This study aimed to determine any signal of regular, low dose morphine on perceived sleep disruption due to breathlessness and perceived sleep quality.

Methods: This is a secondary analysis of data from 38 participants with refractory breathlessness (30 male; 33 with COPD) aged 76 ± 0.9 years who completed a double-blind, randomised, placebo-controlled, cross-over study in which they received 20mg oral sustained release morphine daily and placebo for 4 days each. Participant ratings of sleep disruption due to breathlessness and perceived sleep quality were obtained daily throughout the 8-day trial.

Results: Perceived sleep disruption due to breathlessness over the 4 day period ranged between 13-32% of participants for placebo and 13-26% for morphine, decreasing by each day of the study during the morphine arm. Most participants reported “very good” or “quite good” sleep throughout the trial and were less likely to perceive poor sleep quality during the morphine arm (Odds Ratio=0.55, 95% Confidence Interval 0.34-0.88, $p=0.01$). Participants who reported decreased breathlessness during the 4 days on morphine were also likely to report improved sleep quality with morphine ($p=0.039$).

Conclusions: Four days of low dose morphine improved perceived sleep quality in elderly participants with refractory breathlessness. Regular low dose morphine targeted to reduce refractory breathlessness may yield associated benefits by reducing sleep disruption and improving sleep quality.

Keywords: Opioids, COPD, Sleep-disordered breathing, Sleepiness, Dyspnoea, Controlled clinical trials.

Short Title: Morphine, sleep quality & breathlessness

INTRODUCTION

Refractory breathlessness is a debilitating consequence of cardiopulmonary disease. Treatment of refractory breathlessness is of major importance yet effective treatment options are limited. Regular, daily, low dose oral sustained release morphine ($\leq 30\text{mg}$) is clinically effective and safe in reducing symptoms of breathlessness in people with refractory breathlessness.¹⁻³ However, the mechanisms by which morphine reduces breathlessness are incompletely understood and are likely to be multifactorial. Similarly, the effects of regular, low dose morphine on other key outcomes including sleep quality, which may contribute to changes in perceived breathlessness with morphine, remain largely unknown.

Although morphine has been traditionally prescribed for pain management, its effects on sleep quality and sleep disturbance are unclear. Rather than sleep promotion, acute administration of variable and often quite high doses of morphine (administered orally, intramuscularly and intravenously) in healthy individuals can increase brief awakenings (arousals) and reduce slow wave and rapid eye movement (REM) sleep.⁴⁻⁶ These observations are supported by recent mechanistic studies in rats.⁷

At doses in excess of 30mg/day, morphine may contribute to sleep-related breathing disturbances, particularly central sleep apnoea by a combination of sedation and a reduction in central and peripheral chemoreflex responsiveness.⁸⁻¹³ However, the majority of prior studies in this area have been cross sectional. This is problematic as many patients who are prescribed morphine are taking other centrally acting medications and their co-morbid conditions may also contribute to sleep disruption.¹⁴ As such, there have been very few appropriately designed studies to systematically examine the effect of morphine on sleep quality,¹⁵ particularly at relatively low doses in steady state and in clinically relevant populations such as people with increased respiratory drive due to pain or chronic refractory breathlessness.¹⁶

Conversely, while there is the potential for morphine to disrupt sleep, morphine may actually improve sleep quality and related symptoms in certain patient populations. For example, sleep disruption is common in chronic pain and poor sleep worsens pain perception.^{17, 18} When administered at doses that do not cause respiratory depression, morphine can improve sleep and pain in people experiencing chronic pain.^{19, 20} Recent advances in the understanding of sleep-disordered breathing clearly identify marked heterogeneity in the underlying pathophysiology and the response to opioids.²¹⁻²³

Some central nervous system depressants, including preliminary findings with morphine, that target non-anatomical causes of sleep-disordered breathing can reduce disease severity and improve overnight oxygenation in certain patients.²²⁻²⁴ Thus, morphine may improve respiratory related outcomes in some patients and worsen outcomes in others. Given that the use of morphine and other opioids continues to increase, in conjunction with concerns about serious harms,²⁵⁻²⁹ it is of critical importance to determine if clinically relevant doses of morphine for chronic refractory breathlessness disrupt sleep and, if so, in which patient populations.

In this phase II study we examine the effects of four consecutive days of regular low dose morphine (20mg oral sustained release each morning) compared to placebo in a double-blind, randomised, cross-over study on perceived sleep disruption due to breathlessness and perceived sleep quality in a clinically relevant population of patients with chronic refractory breathlessness.

METHODS

Participants

The data reported in this pilot study are a secondary analysis of 48 participants with chronic refractory breathlessness at rest or on minimal exertion, 38 of whom completed a randomised,

double-blind placebo controlled crossover trial to investigate the effects of morphine on breathlessness.¹ Perceived sleep disruption due to breathlessness at day 4 during placebo and morphine was reported in the parent study.¹ However, none of the other data in the current study has been reported previously. Participants had no history of recent opioid use, no prior adverse reaction to opioids, and no history of substance misuse. All participants' specialists confirmed that reversible factors contributing to breathlessness were optimally treated prior to enrolment. A patient flow diagram is provided in the parent study.¹ Written informed consent to participate in the study was obtained from each participant. The protocol was approved by the Repatriation General Hospital Research Ethics Committee and was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12607000075482).

Protocol and Measures of Sleepiness

Participants were studied over eight consecutive days according to a double-blind, randomised, cross-over design.¹ Participants were randomised to receive either four days of placebo followed by four days of morphine (20mg oral sustained release morphine, Kapanol, Glaxo Smith Kline, Australia) or vice versa. The study medication was taken each morning. There was no wash out period. Two questions relating to perceived sleep quality were assessed daily using patient diary report throughout the trial. Study nurses visited on days 4 and 8 and telephoned on days 2 and 6 to ensure safety, and optimise data collection and study protocol adherence. The specific sleep-related questions assessed throughout the trial were:

1) "Was your sleep disturbed by your breathlessness?" (hereon defined as: "sleep disruption due to breathlessness"; yes/no); and

2) "How was your sleep last night?" (hereon defined as "sleep quality"; four-point scale where 1=very good, 2=quite good, 3=poor, and 4=no sleep).

Daily breathlessness ratings were acquired using a visual analogue scale (VAS) as described previously.¹

Statistical Procedures

Generalized Estimating Equations (GEE) were used to take into account the repeated measures design and correlation between subjects. The model specification was binary logistic (sleep disruption due to breathlessness) or ordinal logistic (sleep quality). The factors included in the models were treatment (morphine vs. placebo), time (in days), and treatment by time interaction effects. An interaction term between treatment and intervention order was also included to test for potential carry over effects and was reported separately in the text. Kruskal-Wallis one way analysis of variance on ranks was used to compare changes in breathlessness (VAS) and sleep quality from day 1 to day 4 during the morphine arm separated into three groups (1. reduction, 2. no change and 3. increase in sleep quality from day 1 to day 4). *Post hoc* comparisons were performed using Dunns' Method. Analyses were conducted using SPSS version 22, SPSS Inc., Chicago, IL and SigmaPlot version 11, Systat Software, Inc., San Jose, CA.

RESULTS

The mean age of the study participants (30 males) was 76 ± 0.9 years. Thirty three of the 38 participants who completed all eight days of the trial had chronic obstructive pulmonary disease (COPD), presenting with breathlessness at rest or on minimal exertion. The remaining five participants with breathlessness had cancer, motor neurone disease, or restrictive lung disease. According to the Eastern Cooperative Oncology Group scale, 71% of the participants were severely restricted (ECOG >2). Twenty eight of the participants were on supplemental oxygen throughout the trial. Twenty of the 38 participants received placebo for the first four days and 18 received morphine for the first four days. Further details of the participant characteristics are reported in the parent study¹. Results from the GEE regression models are presented in Table 1.

Sleep Disruption due to Breathlessness

The percentage of participants who reported sleep disruption due to breathlessness over the 4 day period ranged between 13% and 32% for placebo and 13% and 26% for morphine (Figure 1). The GEE model shows that participants using morphine on day one of treatment (regardless of the allocation order) experienced higher odds of perceived sleep disruption due to breathlessness compared to placebo but the odds decreased by 21% for each additional day of treatment compared to the placebo group as indicated by treatment*time interaction (Table 1). Conversely, the opposite effect was noted during the placebo arm such that the odds of perceived sleep disruption due to breathlessness increased by 27% for each additional day on placebo (Figure 1). There were no carry over effects for sleep disruption due to breathlessness ($p=0.69$).

Sleep Quality

Throughout the trial most participants rated their sleep quality as “quite good” during both arms, while the “no sleep” category was used only once and was therefore collapsed with the “poor” category (Figure 2). There was no significant treatment*time interaction effect (interaction term OR=0.98, 95% CI=0.70-1.36 $p=0.89$). Thus, the interaction term was omitted from the final GEE model. During the morphine arm, participants were less likely to experience poor sleep quality during the morphine arm (OR=0.55; 95% CI=0.34-0.88; $p=0.01$; Table 1). There were no carry over effects for sleep quality ($p=0.71$).

There was significant group effect ($p=0.039$) for change in breathlessness versus change in sleep quality from day 1 to day 4 during the morphine condition (Figure 3). Specifically, the group who reported an improvement in sleep quality from day 1 to day 4 during the morphine arm had a significantly larger reduction in breathlessness compared to the group who reported a reduction in sleep quality.

DISCUSSION

Given the growing evidence base for regular low dose morphine (≤ 30 mg oral sustained release) to treat refractory breathlessness, and its potential to cause impairment and serious harm,²⁵⁻³² it is crucial to accurately determine the effects of clinically relevant repeat doses of morphine on sleep. The findings of the current phase II pilot study indicate that four days of sustained release morphine, at a dose sufficient to reduce symptoms of breathlessness by a clinically meaningful degree,^{1, 3, 33} improves perceived sleep quality in this elderly population of patients with refractory breathlessness.

These findings are intriguing as they suggest that rather than impairing sleep, low doses of morphine targeted to the underlying condition (in this case breathlessness) may actually improve overall sleep quality and could contribute to improvements in symptom perception relating to the underlying condition. Although pain perception was not the focus of the current investigation, the proposed scenario for sleep and breathlessness is consistent with the purported bi-directional relationship in patients suffering from pain in whom strategies to improve pain symptoms (including morphine) can improve sleep, and improved sleep may facilitate further reductions in perceived pain and vice versa.¹⁷⁻²⁰

Recent preliminary findings indicate that a single 30mg sustained release oral dose of morphine does not worsen obstructive sleep apnoea as measured by the apnoea/hypopnea index and can actually improve overnight hypoxemia in certain cases.^{22, 23} These effects are related to changes in ventilatory control and blood morphine concentration, both of which vary greatly between individuals.²¹⁻²³ Similarly, dihydrocodeine reduces peripheral chemosensitivity and oscillatory breathing in patients with chronic heart failure.³⁴ However, patients with COPD who are hypoxic awake and also have sleep-disordered breathing may be particularly vulnerable to severe overnight hypoxemia especially during REM sleep.³⁵ Thus, determining the effects of

clinically relevant doses of morphine on sleep-disordered breathing and overnight oxygenation in patients with COPD is a priority.

Ultimately, achieving the balance between optimal morphine dose to obtain therapeutic benefit for the underlying condition without disrupting sleep nor affecting daytime function will be crucial. While further data are clearly required, the current findings are consistent with ongoing work in pain that suggest that regular low doses of morphine that reduce symptoms of breathlessness,^{1,36} may also yield improvements in sleep quality which could contribute, at least in part, to the observed therapeutic benefit and vice versa. Conversely, in those who experience a worsening of sleep quality with morphine, a reduction in morphine dose or medication cessation should be considered and investigation and treatment of any potential sleep disorder should be undertaken, if clinically warranted.

Methodological Considerations and Recommendations for Future Studies

Strengths of the current approach include the use of rigorous clinical trial design and standardised assessments over several consecutive days including steady-state which is reached in 36 hours using this drug delivery system.

However, this pilot study has several limitations. Firstly, measures of sleep disruption and sleep quality were subjective and were acquired using non-validated assessment tools. Sleep studies were also not performed. Nonetheless, the assessment tools have face validity and given the paucity of data in this area, the current findings provide novel insights to inform larger future intervention trials in which objective measures of sleep and daytime function should be incorporated prospectively.

Perceived sleep quality was also quite high in the current study. Thus, it will also be important to examine the effects of morphine in people who specifically report poor sleep quality in future studies.

The goal of the parent study was to assess the effects of low dose morphine on breathlessness in the steady-state (day 4).¹ This negated the need for a wash out period. We did not find any evidence for carry over effects in the sleep parameters assessed in the current study. Thus, the lack of a wash out period is unlikely to have influenced the current findings. Indeed, the new findings reported in the current pilot study showing gradual reductions in sleep disruption due to breathlessness over 4 days during the morphine arm with corresponding reductions in breathlessness, expand upon and are consistent with the prior findings reported in the parent study of reduced sleep disruption due to breathlessness with low dose morphine versus placebo in steady-state (day 4).¹ Nonetheless, future trials that incorporate additional sleep and alertness measures should include a wash out period or a parallel arm design to avoid any potential carry over effects.

Consistent with a biphasic response, perceived sleep disruption due to breathlessness was relatively high on night one of morphine compared to placebo but steadily decreased thereafter. This pattern suggests that acute sleep disruption may mediate night one effects, at least in part. However, the steady decrease thereafter in the absence of a plateau highlights the clear need to follow patients over time as there is potential for additional benefit beyond the four days tested in the current protocol. Thus, these novel findings challenge previous notions and warrant further investigation.

Summary of Future Research Directions

The current findings pave the way for future studies to explore these proposed relationships in the clinically relevant population of COPD in whom chronic refractory breathlessness at rest or on minimal exertion and sleep disturbances are common.^{35,37} Key priorities for future work will be to incorporate: 1) formal sleep studies, 2) validated and more detailed assessments of sleep, overnight oxygenation and daytime alertness, 3) a longer intervention and assessment period in a larger cohort of participants in whom disease severity and other potential

confounding factors (e.g. nocturnal O₂ therapy, CPAP and other centrally acting medications) are carefully codified and 4) a wash-out period or parallel study design.

Conclusions

In summary, the findings of this pilot study provide insight into the potential effects of clinical use of regular low dose morphine on perceived sleep quality in people with chronic refractory breathlessness. A dose of 20mg of sustained release oral morphine each morning reduced sleep disruption due to breathlessness in a time dependent manner and improved perceived sleep quality. Given the high rates of morphine use and potential for serious harm, these findings add to the data on safety of this clinical intervention. In addition, these findings raise the possibility that reductions in perceived breathlessness with morphine may be mediated, at least in part, by improvement in sleep quality or vice versa.

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Table 1.

Sleep-related outcome measures in a placebo controlled crossover trial of regular low dose morphine (20mg oral sustained release daily) versus placebo in participants with chronic refractory dyspnoea, N=38.

GEE Model	Sleep Disruption due to		Sleep Quality	
	Breathlessness			
Covariates	Binary logistic		Ordinal logistic	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Morphine vs. placebo	3.23 (1.37-7.6)	<0.01	0.55 (0.34-0.88)	0.01
Time (in days)	1.35 (0.94-1.7)	<0.01	0.91 (0.78-1.06)	0.24
Morphine vs. placebo and time interaction	0.58 (0.41-0.84)	<0.01	-	-

GEE= Generalized Estimating Equations, OR= Odds Ratio, CI= Confidence Interval. Refer to the text for further detail.

Figures

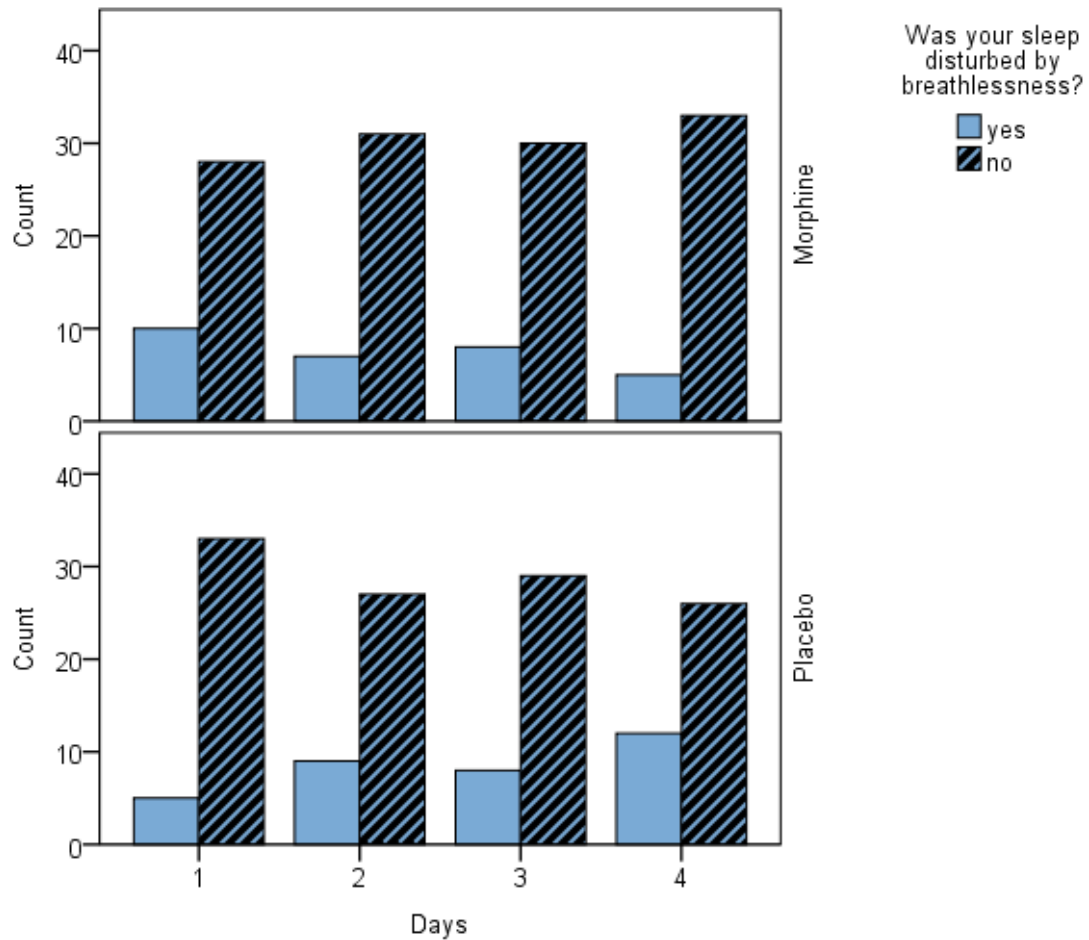


Figure 1. Count of participants who reported sleep disruption due to breathlessness during the 4 days of 20mg oral sustained release morphine and placebo, N=38. There was a significant treatment*time interaction effect such that fewer participants reported breathless related sleep disruption from days 1-4 on morphine whereas the opposite effect was observed during placebo. Refer to the text and Table 1 for further detail.

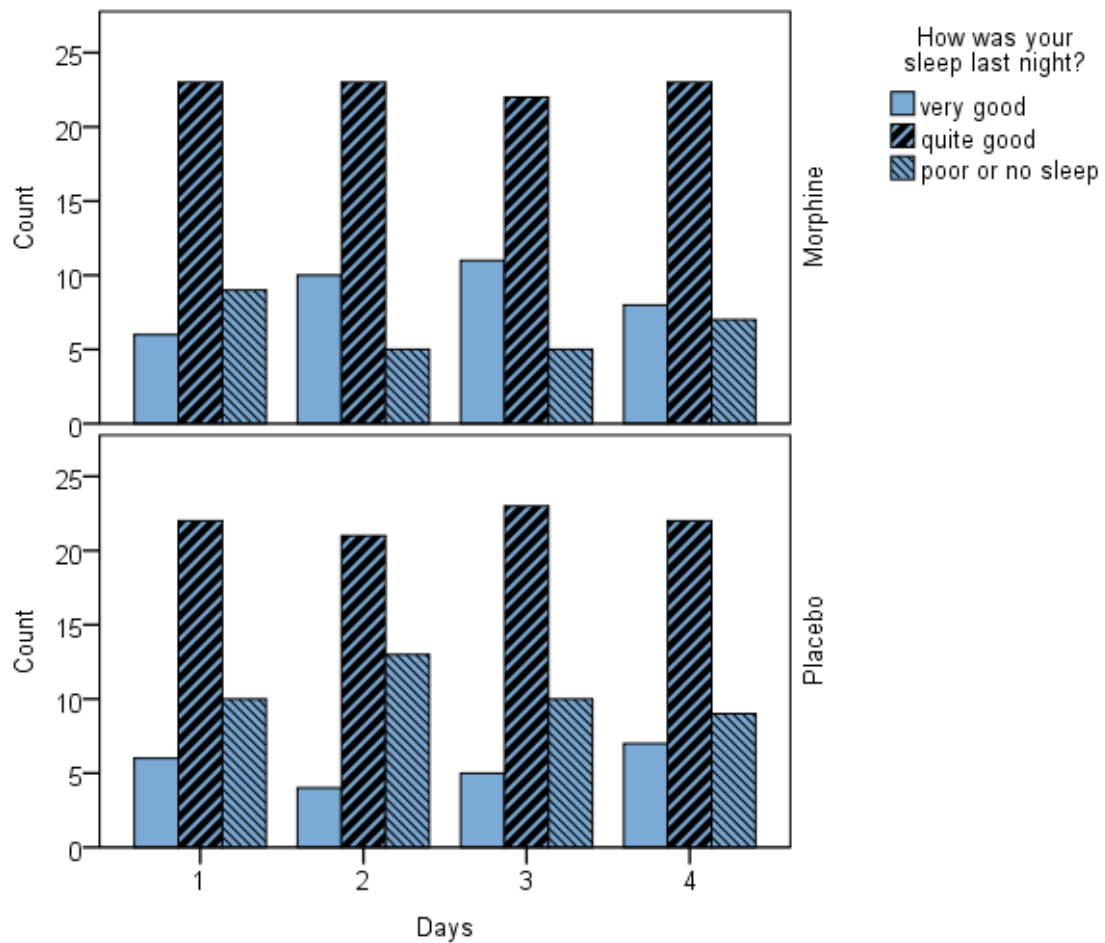


Figure 2. Count of perceived prior night sleep quality during the 4 days of 20mg oral sustained release morphine and placebo, N=38. There was a significant effect of treatment such that participants were less likely to report higher levels of the Likert scale compared to placebo, reflecting lower odds of experiencing poor sleep quality during the morphine arm.

Refer to the text and Table 1 for further detail.

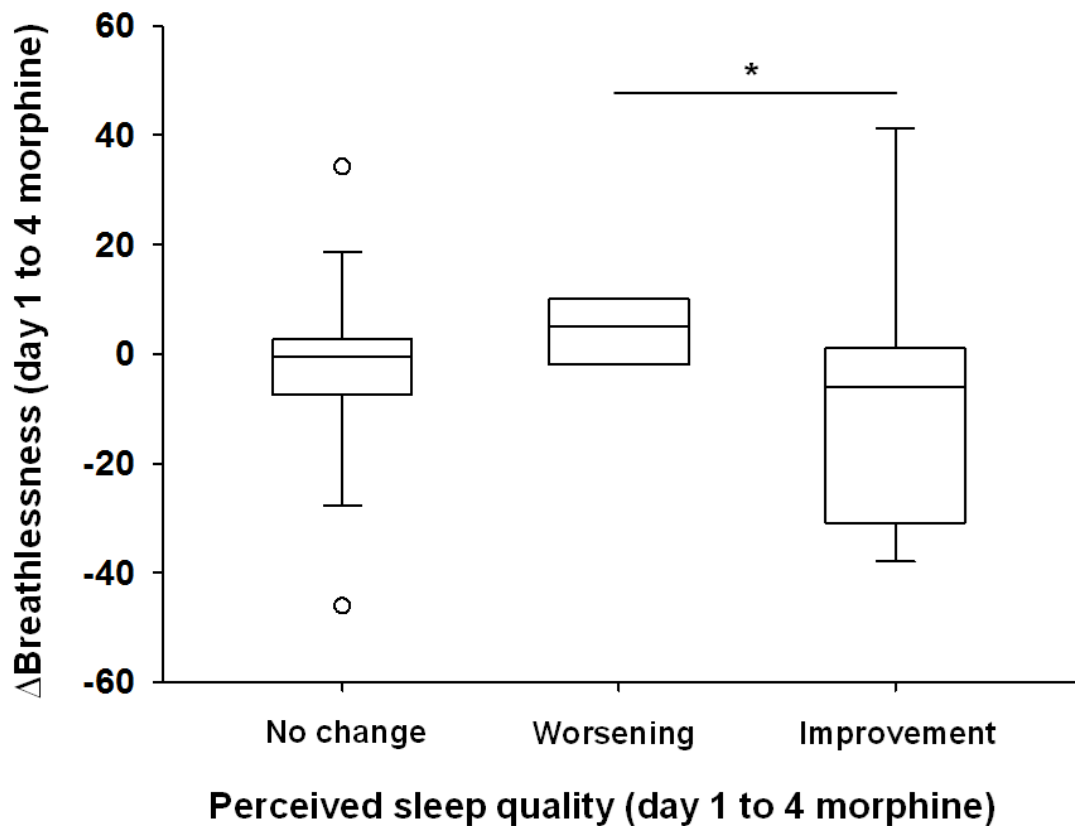


Figure 3. Change (Δ) in breathlessness (visual analogue scale) from day 1 to 4 during the morphine arm according to whether participants reported no change (n=20), worsening (n=7) or improvement (n=11) in sleep quality during the same period. There was a significant group effect ($p=0.039$). * indicates a significant difference between groups ($P<0.05$). Box plots represent median values and 25th and 75th centiles. Whiskers indicate 5th and 95th centiles. Open circles represent data that falls outside these ranges.