Original Article

Once-Daily Opioids for Chronic Dyspnea: A Dose Increment and Pharmacovigilance Study

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Abstract

Context. Randomized controlled trials can answer questions of efficacy, but long-term pharmacovigilance studies generate complementary safety data.

Objectives. Level I evidence supports short-term efficacy of opioids in reducing chronic refractory dyspnea. This study aimed to determine the minimum effective once-daily dose of sustained-release morphine, and whether net clinical benefits are sustained safely.

Methods. In a Phase II dose increment study, 10 mg daily of sustained-release morphine was administered, and increased in nonresponders by 10 mg daily each week to a maximum of 30 mg daily. The participant was withdrawn if there were unacceptable side effects or no response to maximum dose. If participants had a 10% improvement in dyspnea over their own baseline, they joined a long-term Phase IV effectiveness/safety study at that dose. Complying with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, response and side effects are described, with demographic and clinical characteristics of responders.

Results. Eighty-three participants (53 males, mean age 75 years, 54% with chronic obstructive pulmonary disease) provided more than 30 patient-years of data. Fifty-two participants derived ≥10% benefit (on average 35% improvement over baseline), giving a response rate of 62% (number needed to treat of 1.6: number needed to harm 4.6); for 70%, this dose was 10 mg/24 h. Benefit was maintained at three months for 28 (33%) people. Ranking of breathlessness was

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Accepted for publication: December 3, 2010.

0885-3924/$ - see front matter
doi:10.1016/j.jpainsymman.2010.11.021

reduced significantly ($P < 0.001$), but constipation increased ($P < 0.001$) despite laxatives. There were no episodes of respiratory depression or hospitalizations as a result of the sustained-release morphine. Overall, one in three people continued to derive benefit at three months.

Conclusion. Ten milligrams of sustained-release oral morphine once daily is safe and effective for most people who respond. J Pain Symptom Manage 2011;42:388–399.

Key Words
Palliative care, dyspnea, opioids, clinical effectiveness, respiratory

Introduction

Randomized controlled trials can answer questions of efficacy, and although toxicities are reported, these studies are usually of the briefest duration to see a clinical benefit and rarely designed with power to detect significantly different levels of toxicities, especially if they are rare. The optimal way to answer questions of safety, sustained benefits, and long-term toxicities is through ongoing pharmacovigilance studies to understand the net clinical benefit in everyday practice. Pharmacovigilance studies are, by definition, uncontrolled studies.

Dyspnea is more than a sentinel clinical sign; dyspnea, experienced acutely or chronically, threatens a person's very existence, psychological well-being, and social functioning. Once reversible causes of dyspnea have been addressed, residual symptomatology is "refractory dyspnea."[1]

At a population level, refractory dyspnea is a significant chronic burden for a sizeable number of individuals.[2,3] Moreover, with many respiratory, cardiac, hematological, oncological, and neuromuscular disorders, breathlessness is likely to worsen over time.[4] There are no symptom-specific medications to treat refractory dyspnea registered with pharmaceutical regulatory bodies such as the U.S. Food and Drug Administration, the European Medicines Evaluation Agency, or the Australian Therapeutic Goods Administration.

Evidence, including an adequately powered randomized study and a meta-analysis, demonstrates that opioids reduce the intensity of refractory breathlessness.[1,5] The effect of opioids on the subjective sensation of breathlessness is further supported by recent evidence demonstrating that blockade of endogenous opioids during exercise worsens the perception of breathlessness without changing the ability to exercise in people with chronic obstructive pulmonary disease (COPD).[6]

The American College of Chest Physicians has recently released a position paper endorsing the use of opioids for people who have breathlessness "that persists at rest or with minimal activity."[7] Although data supporting opioids for the treatment of refractory dyspnea are clear, studies to date have not yet defined the minimum effective once-daily dose.[1,8,9] Furthermore, since the study by Abernethy et al., which evaluated the efficacy of 20 mg oral morphine daily, a 10 mg/24 h preparation has become available.

Prospective data about long-term safety of opioids for refractory dyspnea are lacking. Many clinicians continue to extrapolate from the acute toxicity witnessed when frail or infirm patients who were opioid-naïve were administered opioids in the emergency room or postoperatively, with severe side effects including confusion, drowsiness, and respiratory depression.[10,11] These observations, first made more than six decades ago, still largely underpin the poor uptake of an entirely different way of prescribing opioids for refractory breathlessness—regular low doses orally. International guidelines for opioids in refractory breathlessness continue to reflect concerns generated by the way opioids are used for acute pain.[12,13] Lack of dosing and safety data continue to be one barrier in the registration of a dyspnea-related indication for morphine.

Given the chronic nature of breathlessness for many people, there are justifiable concerns that benefits of opioids may diminish over time. There have been no longitudinal prospective data describing the net clinical benefits of

low-dose opioids in people with chronic refractory dyspnea.

The aims of the Phase II exploratory, open-label, dose-ranging study were to define the minimum once-daily dose of morphine for reducing chronic refractory dyspnea by ≥10%; a Phase IV follow-on study sought to define the safety and long-term effectiveness of daily sustained-release morphine. The best level of evidence for Phase IV outcomes is generated by prospective cohort data collection. Results complement current Phase III evidence about the short-term efficacy of opioids in relieving chronic refractory breathlessness.

Methods

Study Design

This study comprised Phase II and Phase IV components (Fig. 1). Phase II was an open-label prospective study of once-daily sustained-release opioid (morphine sulfate 10 mg/24 h titrated weekly by 10 mg/24 h in nonresponders up to a maximum of 30 mg/24 h) administered with laxatives (sodium docusate with sennosides). If at any weekly review the participant had a reduction of ≥10% over baseline in dyspnea intensity without unacceptable side effects, they entered the long-term safety and effectiveness Phase IV study. Any unresolved significant side effects at any time, or a lack of response by the end of the three-week titration during the Phase II component of the study resulted in participant withdrawal.

Study Participants

Participants were opioid-naïve outpatients with a palliative diagnosis, aged ≥18 years, and with ongoing dyspnea, scored at 3 or 4 on the modified Medical Research Council (MMRC) Dyspnea Scale[14] (Table 1). Any underlying reversible causes of the dyspnea

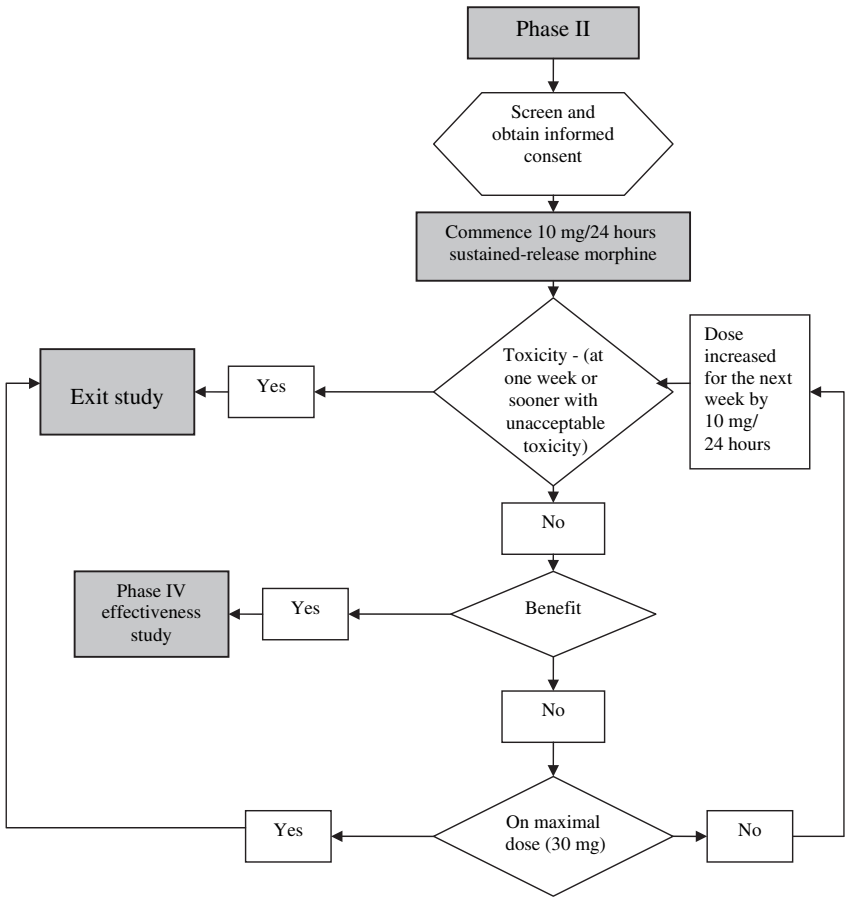

Fig. 1. Schema for participant flow in a Phase II and Phase IV open-label dose-ranging study of once-daily sustained-release morphine in people with refractory dyspnea.

Table 1
Modified MRC Dyspnea Scale[13]

Grade	Description of Symptom
0	"I only get breathless with strenuous exercise"
1	"I get short of breath when hurrying on the level or walking up a slight hill"
2	"I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"
3	"I stop for breath after walking about 100 yards or after a few minutes on the level"
4	"I am too breathless to leave the house" or "I am breathless when dressing"

MRC = Medical Research Council.
Note: This modified MRC scale uses the same descriptors as the original MRC scale in which the descriptors are numbered 1–5.

must have been maximally treated, as assessed by a consultant physician whose area of practice was most relevant to the cause of this person's dyspnea (e.g., a cardiologist for someone with cardiomyopathy). Participants must have been on stable medications and oxygen (if required) for the seven days before commencing the study, with an estimated prognosis of more than one month.

Exclusion criteria included regular use of any opioid medication in the two weeks before screening, a true hypersensitivity reaction to opioids, a history of substance misuse, use of monoamine oxidase inhibitors in the last two weeks, functional status less than 50 on the Australian-modified Karnofsky Performance Scale (AKPS)[15] (Table 2), a calculated creatinine clearance of less than 15 mL/min (as calculated using the Modification of Diet in Renal Disease formula[16]), pregnancy, confusion (less than 24/30 on a Mini-Mental State Examination[17]), or unwilling or unable to complete the study measures.

Settings

Participants were recruited from four tertiary university teaching hospitals in two states of Australia between July 2007 and October 2009. Data collection was completed in January 2010. Lead study investigators were respiratory and palliative medicine physicians, although referrals were encouraged from all disciplines including cardiology and oncology.

Study Withdrawal

Withdrawal from the study could be initiated at any time by the participant. Other reasons for withdrawal included AKPS[15] falling below 30, a sudden increase in dyspnea, or participant death.

Measurements

Intensity of dyspnea was the primary outcome, measured as subjective breathlessness on a 100 mm visual analogue scale (VAS) "right now" (hence, at rest) anchored at 0 mm as "no breathlessness" and at 100 mm as "worst imaginable breathlessness." Participants recorded dyspnea twice daily in a purpose-printed diary. Secondary outcomes included the McGill Quality of Life (MQOL) Questionnaire.[18] All

Table 2
Characteristics of 83 Participants Who Provided More Than 30 Patient-Years of Data on Opioids for Refractory Breathlessness

Characteristic		*n*	%
Gender	Male	53	64
Diagnosis	Chronic obstructive pulmonary disease	45	54
	Cancer (primary lung; $n = 19$)	24	29
	Interstitial lung disease	10	12
	Other causes	4	5

	Mean	SD	Median	Range
Age	74.6	9.1	76.5	51–88
Dyspnea intensity score (100 mm visual analogue scale)	50.3	19.4	55.3	7–86
Modified Medical Research Council Scale	3.8	0.4	4.0	3, 4
Australian-modified Karnofsky Performance Status (0–100)	63.5	9.2	60.0	50–80
Body mass index[a]	25.2	5.8	24.5	14.2–46.5
McGill quality of life global rating (0–10)	5.9	2.1	6.0	0–10
Participation in study (days)	142.4	190	29	2–665

[a]Not available for six participants.

demographic and clinical data were collected by dedicated research staff.

During the Phase II dose-ranging substudy (83 participants), morning and evening dyspnea VAS scores recorded on days 5–7 of each seven-day week (i.e., during steady-state) were averaged and contributed to assessments of the number of people who responded to morphine and the dose at which they responded; an individual improvement of 10% over baseline was considered, a priori, as a clinically significant improvement, consistent with previous studies of similar interventions.[1,5]

During the Phase IV long-term effectiveness component of the study (52 participants), the number of people still on opioids at three months, the dose of opioid at three months, and the number of dose changes since entry to this substudy were recorded. Side effects at any time causing cessation of the medication were a key secondary outcome.

Data Collection and Data Quality

Data were collected, coordinated centrally by the lead site, and entered contemporaneously on a customized 128-bit secure web-based research data management system (www.caresearch.com.au) so that any discrepancies could be addressed immediately.

Sample Size

Given the overall health of the target population, it was expected that, on average, individuals would participate for three months, and with up to 100 participants, that would generate 25 patient-years of data in the Phase IV arm. The figure of 25 patient-years of data was arbitrarily chosen, seeking to reflect the broad population likely to be prescribed opioids in the setting of the palliation of refractory breathlessness.

Analysis

Basic descriptive statistics were used to define the population and their response to opioids. Intensity of breathlessness was described at baseline, at completion or withdrawal from the Phase II dose-ranging period, and at three months or the last recorded level in the long-term Phase IV effectiveness period. Comparisons were made of key demographic and clinical factors for people who did and did not progress to the Phase IV study using Chi-square tests. Significance was assumed at $P < 0.05$. A comparison of the number of people who rated breathlessness or constipation as one of their problems at the beginning and end of the study was made using the McNemar test with continuity correction. To confirm the direction and magnitude of primary outcome, data were reanalyzed using 15% and 20% improvements in dyspnea at the end of Phase II. The numbers who need to be treated to get one response (number needed to treat) is the total number of participants divided by responders. Conversely, the number needed to harm is the total number of participants who withdrew directly because of toxicity as a function of all participants.

Ethics, Consent, and Trial Registration

The research was approved by all participating institutions' research and ethics committees. All participants provided written informed consent before participating in the study. The study received Clinical Trials Notification approval to use Kapanol™ (GlaxoSmithKline, Boronia Park, Victoria, Australia) for an unregistered indication. The trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRNO12606000269538).

Reporting

This article complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting requirements for observational studies.[19]

Results

Participant Flow and Study Population

A total of 202 patients with dyspnea were screened, and 83 participated in the study as outpatients (Fig. 2). Fifty-three participants (64%) were male, and 45 (54%) had COPD as the underlying cause of their breathlessness. Age ranged from 51 to 88 years (mean 74.6; standard deviation [SD] 9.1), with a median AKPS of 60, meaning that at least half of the participants required someone else's help with some activities of daily living. Duration of participation in the study was a mean of 142 days (SD 190; median 29; range 2–665; Table 2).

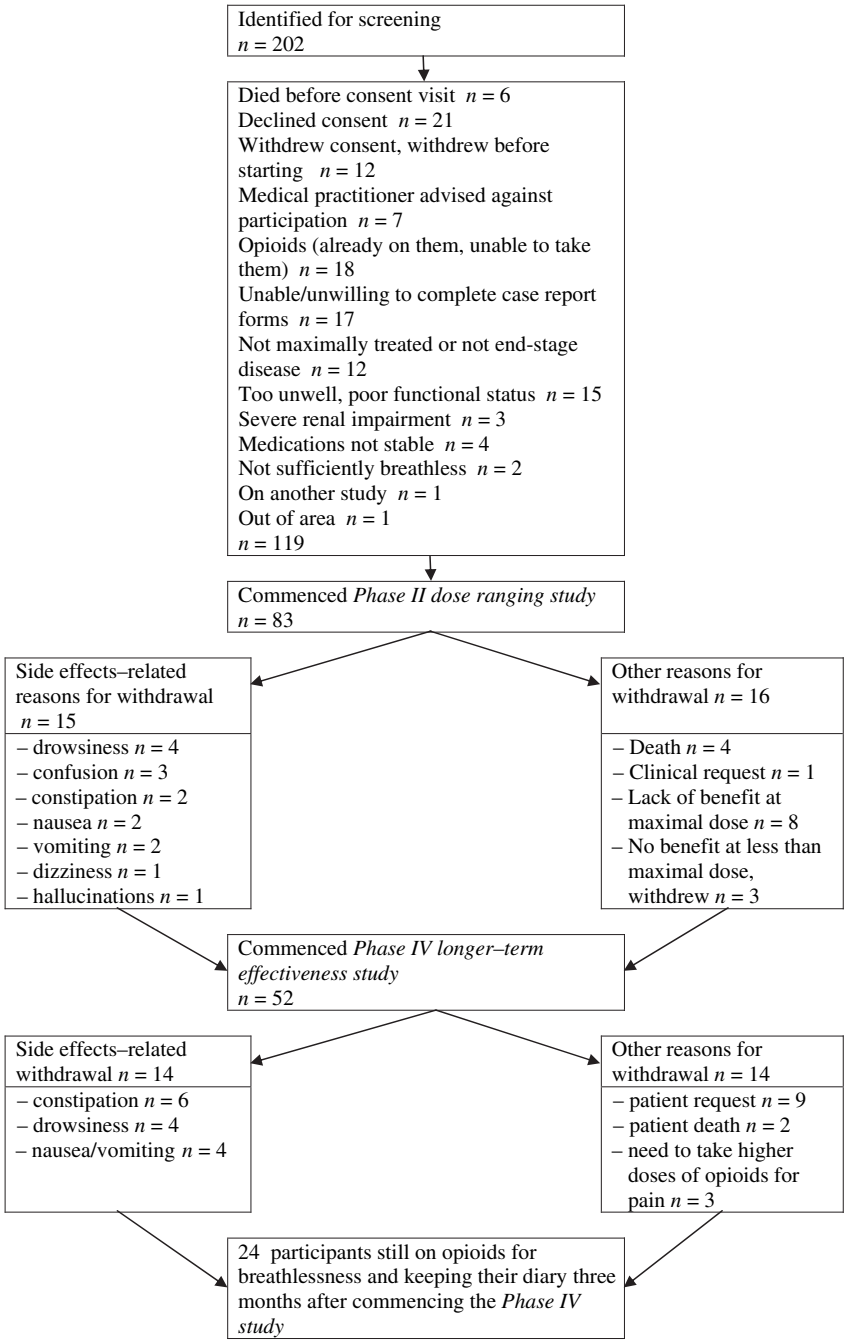

Fig. 2. Participant flow diagram for Phase II dose ranging and Phase IV continued clinical effectiveness study for once-daily sustained-release morphine in refractory dyspnea.

Phase II Dose Ranging

At the end of the Phase II period, the average VAS score for intensity of dyspnea from baseline (in the two days before medications commenced) of 50.3 mm (SD 19.4; median 55.3; range 7–86) had fallen to 40.0 (SD 20.3; median 39.8; range 2–87). Including all 83 participants, the mean sustained-release morphine dose was 16.5 mg (SD 8.0; median 10.0). Thirty-one participants either derived no benefit at the maximum dose of 30 mg of sustained-release morphine ($n = 8$), lacked benefit at other doses ($n = 3$), had unacceptable side effects ($n = 15$), or withdrew for

reasons other than the therapy (death $n=4$ [two to six (median 4.5) days after commencing therapy] and clinical request $n=1$) (Fig. 2; Table 3). For the 15 with unacceptable side effects, these included drowsiness ($n=4$), confusion ($n=3$), and constipation ($n=2$) (Fig. 2), all of which reversed rapidly with cessation of medication and occurred between two and 21 (median 13) days after commencing therapy. No one required hospitalization for any toxicity.

On an intention-to-treat basis, the response rate at the end of the Phase II period was 52 of 83 (63%), giving a number needed to treat of 1.6, and a number needed to harm of 4.6. If in Phase II, the threshold indicating a successful therapeutic response was increased to 15% or 20% over baseline dyspnea scores, then 42 individuals (51%) and 34 individuals (41%), respectively, would have met these revised response criteria. No significant differences in response were seen by baseline breathlessness or by diagnosis (Table 3). Other factors that did not predict progression to Phase IV included gender, age (≤75 years or older), baseline VAS severity (≤60 or greater), AKPS (40, 50 vs. ≥60),[15] MQOL Questionnaire at baseline (≤5 vs. >5),[18] or body mass index (≤25 vs. >25). Because potential univariate predictors were not significant, a multivariate model was not created.

Phase IV Long-Term Effectiveness

For the 52 participants who derived at least a 10% improvement over their own baseline breathlessness without unacceptable side effects, the average dose of once-daily sustained-release morphine entering Phase IV was 14.0 mg (SD 6.3) (Table 4). In this subgroup, 69.2% had benefit at 10 mg of sustained-release morphine in 24 h, 23.1% at 20 mg, and 7.7% at 30 mg. For people entering the Phase IV substudy, the average improvement in scores from their own baselines as they entered Phase IV was 17.1 mm (SD 11.6) (Table 4). A total of 29.9 years of data were collected in the Phase IV period (mean 209.5 patient-days per participant entering the Phase IV period) within a total of 32.4 patient-years of data overall (Phase II and Phase IV).

Withdrawal from the Phase IV study included 13 people who withdrew because of unacceptable side effects (constipation [$n=6$], drowsiness [$n=4$], and nausea and vomiting [$n=4$]) (Fig. 2) within the first three months. All unacceptable side effects settled rapidly with cessation of opioids, and no hospitalizations were required. Additionally, three participants required increased opioid doses for pain, two participants died as a result of disease progression during follow-up, and three identified that clinical benefit had waned. One participant had a single episode of urinary retention that did not necessitate study withdrawal but may have been caused or exacerbated by the anticholinergic effects of morphine.

At three months after commencing Phase IV, of the 24 people still taking opioids for breathlessness and keeping a diary, 12 were taking 10 mg of sustained-release morphine per 24 h and 12 were taking 20 mg. Nineteen were on the same dose from which they left the Phase II dose-ranging study period, four had increased their dose by 10 mg/24 h, and one had decreased the dose by 10 mg/24 h. Another four participants continued on their sustained-release opioid but did not continue their diary.

Patient-Identified Problems—Breathlessness

Using any of the first three ranked problems identified by participants on the MQOL Questionnaire at baseline and on completion of the study or withdrawal, there was a significant decline in reports of breathlessness and a significant increase in the number of people who were constipated (Table 5).

Toxicity. No study participants presented to health care providers: none were hospitalized for respiratory depression, decreased level of consciousness, or delirium. People who chose to cease their sustained-release morphine because of lack of effect or unacceptable side effects did so without a withdrawal syndrome.

Discussion

This study confirms that many people respond to opioid therapy when administered for chronic refractory breathlessness, and that for some this benefit can be maintained over time. Despite concerns about treating infirm elderly individuals with opioids, study participants

Table 3

Baseline Modified MRC Scale and Diagnosis by Visual Analogue Scale Baseline Response and Progress Through the Study

		VAS Intensity of Dyspnea at Baseline	Difference—First and Last Measured VAS in Phase II	Progress Through Study		
		Average *Standard Deviation* *Median* *Range*	Average *Standard Deviation* *Median* *Range*	Proceeded to Phase IV	Withdrew: Toxicity	Withdrew: Other Reason
MMRC Scale at baseline	3 ($n = 20$)	48.4 *20.1* *51.0* *9–83*	13.5 *18.5* *11.5* *−32 to 46*	15 (79%)	1	3
	4 ($n = 63$)	47.7 *21.7* *51.0* *6–85*	5.2 *19.9* *6.0* *−46 to 61*	37 (59%)	14	12
Dominant underlying cause of dyspnea (n; %), with MMRC 3 at baseline	COPD ($n = 45$; 25%)	50.0 *22.6* *58* *7–83*	8.7 *16.6* *11* *−38 to 43*	32 (71%)	7	6
	Cancer ($n = 24$; 24%)	44.2 *22.1* *48.5* *6–85*	4.2 *19.3* *5.8* *−33 to 46*	14 (58%)	4	6
	Interstitial lung disease ($n = 10$; 20%)	44.8 *15.4* *51.5* *18–61*	3.2 *32.7* *3.9* *−46 to 61*	4 (40%)	4	2
	Other causes[a] ($n = 4$; 25%)	53.3 *9.4* *56* *40–62*	17.7 *15.7* *19* *0 to 33*	3 (75%)	—	1

[a]Heart failure:1; bronchiectasis:1; pulmonary hypertension:1; bronchiolitis obliterans organizing pneumonia:1.

Table 4
Phase IV Long-Term Effectiveness Study of People Who Have Responded to Once-Daily Sustained-Release Morphine for Refractory Dyspnea ($n = 52$)

Characteristics at Beginning of Phase IV	Mean	SD	Median	Range
VAS as participants enter Phase IV study	34.4	17.2	37.8	1.8–70.5
Improvement (mm on VAS entering Phase IV study) from baseline	17.1	11.6	13.3	2.2–61.6
Individual percentage improvement over baseline entering Phase IV study[a]	35.2	21.3	30.1	10.1–85.7
Dose of sustained-release morphine (mg/24 h) entering Phase IV	14.0	6.3	10.0	10–30

[a]Equals baseline dyspnea minus final dyspnea divided by baseline dyspnea.

did not encounter severe toxicity; although side effects did occur, these resolved rapidly with treatment or cessation of medication.

It needs to be emphasized that the way opioids have been used in this study is distinctly different to the way that they are used for acute pain in opioid-naïve patients. Opioids were administered as around-the-clock steady-state dosing, more consistent with the management of chronic pain in opioid-tolerant patients.

Is the reduction in breathlessness clinically significant? In acute decompensation (acute heart failure, acute asthma), it is likely that a two-point reduction on a 0–10 numerical rating scale is required before patients discern any appreciable difference.[20,21] By contrast, in chronic breathlessness, evidence from patient-derived data[22] and consensus[23] suggests that a one-point reduction in the intensity of breathlessness is clinically meaningful for patients. The level of breathlessness seen in this present study is of the same order of magnitude as several recent studies in refractory breathlessness.[1,24,25] Beyond evaluating whether patients consider the net clinical benefit sufficient to continue a therapy, a clinically minimally important difference can be explored statistically.[26] A reduction in an observation by a level greater than 50% of the SD of the original observation is likely to be meaningful in measures such as quality of life and potentially in other biological models.[27] In this study, the initial SD of the intensity of breathlessness on a VAS was 19.8 mm, so any reduction of greater than 9.9 mm would exceed a 50% reduction in the SD of the initial observation. The overall reduction in breathlessness for all 83 participants (responders and nonresponders) at the end of the titration period was 10.3 mm on the VAS, or a 20.4% reduction, suggesting that this is likely to be clinically significant.

Of interest is the finding of VAS compared with MMRC at baseline. Despite different levels of exercise tolerance before breathlessness is generated, the VAS scores between these two groups is absolutely identical. This supports that concept that several dimensions of breathlessness need to be measured to generate a full picture of the symptom and its effect on the lives of those experiencing it.

What Other Conclusions Do These Data Support?

These data are consistent with a mediating role of opioids in people with refractory dyspnea without compromising respiratory function,[6,28] and with Phase III studies that have

Table 5
Participant-Ranked "Physical Symptoms or Problems That Have Been the Biggest Problem for You Over the Past Two Days" at Baseline and When Last Recorded from the MQOL Questionnaire

Symptom	First-Ranked Symptom Concern	*P*-value[a]	Symptom of Concern Ranked in the Top Three	*P*-value
Breathlessness				
Baseline $n = 83$	74	<0.001	79	<0.001
Last recorded $n = 81$[b]	39		55	
Constipation				
Baseline $n = 83$	0	<0.001	7	<0.001
Last recorded $n = 79$[b]	12		25	

[a]McNemar Chi-squared test with continuity correction.
[b]Four participants died during the initial titration for reasons unrelated to the study medication, and one person withdrew before taking any medication.

been reported to date.[1,5] This present study supports the use of opioids for longer periods of time with no clinically significant respiratory compromise and no evidence of tachyphylaxis. Taking mMRC as an index of function before breathlessness occurs, as with a previous study, there is a trend that supports that those with higher functional status derived more benefit from opioids for chronic breathlessness[29] (Table 3).

Do These Findings Differ From Any Other Reported Data?

These data challenge widely held beliefs that opioids should not be used in people with respiratory compromise. Such beliefs are *not* based on data from people on regular low-dose opioids. No study participant had an episode of respiratory compromise. The data also challenge concerns about the withdrawal of opioids when cessation is clinically indicated.

Strengths of the Study

The study, spread across four sites with differing referral patterns, can be extrapolated to other clinical settings. The study followed people closely throughout the time that they were on opioids, without loss to follow-up. The primary outcome measure of intensity of breathlessness reflects the primary concern of people with ongoing refractory breathlessness.

Limitations of the Study

Design. The threshold of 10% for response was arbitrary and not averaged over several days. When other thresholds were considered in a sensitivity analysis (15% and 20%), there were still a substantial number of people who derive benefit from opioids. The absence of end-tidal carbon dioxide measurement or oxygenation is unfortunate, but the absence of significant respiratory compromise is reassuring. However, the study was designed during a time when easily portable, affordable, community-based assessment of end-tidal carbon dioxide was not available, and it was felt that the burden of arterial blood gas measurements in this patient group was not supportable. Dose titration stopped at 30 mg per 24 h, given the levels of toxicity reported in an earlier study that used higher doses of opioids in the chronic setting.[30] Given the small number of people (8/83) who did not benefit at 30 mg daily without toxicity, further escalation is unlikely to significantly improve response rates.

These results may under-represent the net clinical benefit. As with pain, people may increase activity as the symptom is better controlled but report only marginal improvement in the symptom itself. As such, future work in this area needs to have a meticulous understanding of differential changes in functional status over each person's own baseline, including an objective measure of exertion around the clock.

Sample. This is a group of people with a variety of underlying pathophysiologies causing refractory breathlessness. Although the underlying pathophysiology generating breathlessness may differ, there are no data to support that the central common pathways where μ-opioid receptors modulate the sensation are specific to any particular disease states. People with heart failure are under-represented in the sample, and given encouraging evidence that they may be a diagnostic group who may respond well to opioids for their refractory dyspnea, this is not ideal.[24,29] The sample deliberately did not engage people with acute exacerbations of breathlessness, although this would be an area for future research.

Generalizability

This study represents findings from several sites with people whose unifying feature is the severity of their breathlessness. Fundamentally, there is a question of whether underlying pathologies generate distinct types of breathlessness that are equally responsive to opioids. Whether the underlying etiology of breathlessness is sufficiently uniform to allow interchangeability of symptomatic therapies between differing pathologies is not finally determined. The predominant diagnosis was people with COPD, the area in which most work has been done in breathlessness to date.[6,31]

Implications for Clinicians and Policymakers

This study adds to the weight of evidence that opioids can be used judiciously in people with refractory breathlessness without compromising their health. Benefit was sustained in more than half of the people who gained an

initial response without unacceptable side effects. One-third of all people who commenced therapy derived long-term benefit, suggesting that although there is a group of responders, more work needs to be done to find optimal therapies for breathlessness. Given that there are no medications registered for the treatment of breathlessness, opioids are still the best starting point for therapy. Most clinical follow-up was done by general practitioners in the community, and these should be the practitioners who manage dyspnea using opioids in the future.

Unanswered Questions and Future Research

These data support the need for a subsequent study exploring whether incremental dose increases in opioid responders would provide further symptom relief and hence a dose-response relationship. This design would require that people could reduce dose with toxicity if they had derived benefit at a lower dose. Future work with opioids also needs to distinguish between changes in the intensity of breathlessness and the unpleasantness that it engenders and to seek to compare the net clinical benefit of different opioids. Noninvasive measures of changes in the partial pressure of carbon dioxide and oxyhemoglobin saturation in the first days of dose initiation or dose increment should be monitored.

The study highlights a key challenge for many new therapies—it is not practicable to power adequately rigorous studies for an expected but extremely rare toxicity such as respiratory depression. This study underscores the need for good, publicly available, and routinely collected pharmacovigilance studies for all therapies, including opioids in breathlessness.[32]

Disclosures and Acknowledgments

This study was generously supported by National Health and Medical Research Council grant #480459. The authors declare no conflicts of interest.

Thanks go to all of the participants who gave their time. Thanks also go to Ms. Debbie Marriott for her expertise in manuscript formatting and submission, and to Ms. Aine Greene and Ms. Heather Griggs for their help with the data.

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