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ORIGINAL ARTICLE

Real-world opioid prescription to patients with serious, non-malignant, respiratory illnesses and chronic breathlessness

Xinye Chen [1], Thomas Moran [2] and Natasha Smallwood [3,4]

[1]Department of Medicine, Eastern Health, [2]Department of Medicine, The Royal Melbourne Hospital, [3]Department of Respiratory Medicine, The Alfred Hospital, and [4]Department of Allergy, Immunology and Respiratory Medicine, Central Clinical School, The Alfred Hospital, Monash University, Melbourne, Victoria, Australia

Key words
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Correspondence
Natasha Smallwood, Department of Respiratory Medicine, The Alfred Hospital, 55 Commercial Road, Melbourne, Vic. 3004, Australia.
Email: natasha.smallwood@monash.edu

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Abstract

Background: Chronic breathlessness is a disabling symptom that is often under-recognised and challenging to treat despite optimal disease-directed therapy. Low-dose, oral opioids are recommended to relieve breathlessness, but little is known regarding long-term opioid prescription in this setting.

Aim: To investigate the long-term efficacy of, and side-effects from, opioids prescribed for chronic breathlessness to patients with advanced, non-malignant, respiratory diseases.

Methods: A prospective cohort study of all patients managed by the advanced lung disease service, an integrated respiratory and palliative care service, at the Royal Melbourne Hospital from 1 April 2013 to 3 March 2020.

Results: One hundred and nine patients were prescribed opioids for chronic breathlessness. The median length of opioid use was 9.8 (interquartile range (IQR) = 2.8–19.8) months. The most commonly prescribed initial regimen was an immediate-release preparation (i.e. Ordine) used as required (37; 33.9%). For long-term treatment, the most frequently prescribed regimen included an extended-release preparation with an as needed immediate-release (37; 33.9%). The median dose prescribed was 12 (IQR = 8–28) mg oral morphine equivalents/day. Seventy-one (65.1%) patients reported a subjective improvement in breathlessness. There was no significant change in the mean modified Medical Research Council dyspnoea score ($P = 0.807$) or lung function measurements ($P = 0.086$–0.727). There was no association between mortality and the median duration of opioid use ($P = 0.201$) or dose consumed ($P = 0.130$). No major adverse events were reported.

Conclusion: Within this integrated respiratory and palliative care service, patients with severe, non-malignant respiratory diseases safely used long-term, low-dose opioids for breathlessness with subjective benefits reported and no serious adverse events.

Introduction

Advanced, non-malignant, respiratory diseases, such as chronic obstructive lung disease (COPD) and interstitial lung disease (ILD), are progressive debilitating conditions associated with increased morbidity, mortality and healthcare burden.[1,2] COPD is the third leading cause of death worldwide and the fifth in Australia.[1,3] ILD are less common and include of a variety of conditions, yet remain challenging to manage, due to the highly heterogeneous clinical course and limited therapeutic options.[4]

Breathlessness is a predominant and distressing symptom in patients with advanced, non-malignant, respiratory diseases, which causes high levels of disability, reduced quality of life, and significant distress to patients and their carers.[5,6] Approximately 40–95% of COPD patients experience moderate-to-severe persistent breathlessness despite disease-directed therapy,[5,7–10] and severe breathlessness is associated with a worse prognosis.[11] Compared with patients with lung cancer, patients with advanced respiratory diseases live longer, and suffer from more severe and sustained breathlessness throughout the disease journey.[5,12,13] As the illness progresses, chronic breathlessness becomes so common that it may be overlooked or overshadowed by other severe symptoms, such as pain.[14–16] As chronic breathlessness is under-recognised and

undertreated,[10,16–20] the term 'chronic breathlessness syndrome' was proposed in order to highlight the need for active assessment and treatment of this debilitating symptom.[18,21]

To cope with severe chronic breathlessness, patients with advanced respiratory diseases, often become more sedentary and have reduced social contact outside the home, both of which further limit their function and quality of life.[21,22] Active management approaches for severe chronic breathlessness should be individualised and include optimising the treatment of all underlying contributing illnesses, non-pharmacological strategies (such as breathing exercises, postures to reduce dyspnoea, activity pacing and fan therapy to the face) and palliative pharmacological measures (opioids).[23] Oral opioids are recommended in Australian and international guidelines to relieve breathlessness in patients with advanced lung diseases,[14,24–26] as there is some evidence that regular, low-dose (up to 30 mg daily) oral morphine may safely relieve chronic breathlessness.[27–31] However, most clinical trials to date have been of short duration (weeks) and mainly included stable people with COPD in the outpatient setting. Importantly, two recent randomised, placebo-controlled trials showed no effect of opioids on breathlessness over 1–4 weeks.[31,32] These conflicting findings may be explained by the unpredictable trajectory of advanced lung diseases and the heterogeneous patient groups included (with some trial patients having only moderate dyspnoea) due to challenges recruiting to trials. Nevertheless, little is known about the long-term benefits and harms from opioids prescribed for chronic breathlessness.[33] Therefore, prospective, longitudinal studies are needed, ideally in real-world clinical practice settings.[28] This study aimed to investigate the benefits and side-effects of opioids prescribed for severe chronic breathlessness to patients with advanced respiratory diseases over some years.

Methods

Study design

A prospective cohort study was conducted, including all patients with advanced, non-malignant respiratory diseases who were being managed by the advanced lung disease service (ALDS) at the Royal Melbourne Hospital (RMH) from 1 April 2013 onwards. RMH is a tertiary referral, metropolitan, teaching hospital and the ALDS is an integrated, multidisciplinary, outpatient respiratory and palliative care service, which was established in April 2013. The ALDS aims to provide long-term, holistic, patient-centred care for people with severe, non-malignant, respiratory lung diseases.[34]

Data were collected prospectively for all ALDS patients, with only data from patients who were prescribed opioids reported in this manuscript. The patients were divided into two groups according to the indications for opioid use:

1 Patients prescribed opioids for the management of severe chronic breathlessness, including patients taking opioids for breathlessness only, or for both breathlessness and pain;
2 Patients prescribed opioids for indications other than breathlessness, for example, for pain relief only.

The comparison of these two groups enabled us to understand whether patients taking opioids for different clinical indications shared similar risk factors that predisposed them to opioid-related adverse events. Patients prescribed opioids for the management of severe chronic breathlessness were the primary focus of this study.

Data were collected from the ALDS clinic management database, paper files and electronic medical records. The period of inclusion for this study was 1 April 2013 to 3 March 2020 (i.e. study census date, at which no further information was collected). Collected data included: patient demographics, smoking history, primary respiratory diagnosis, comorbidities, most recent respiratory function results and mortality data. For patients who were prescribed opioids for breathlessness (group 1), further data were collected regarding pharmacological and non-pharmacological management of their respiratory conditions, multidisciplinary specialist input, exacerbation frequency and opioid regimen for breathlessness.

Breathlessness severity was measured sequentially at each clinic visit with the five-point modified Medical Research Council (mMRC) dyspnoea scale and through a subjective dichotomous question (yes/no) question regarding whether breathlessness had changed since the last intervention (e.g. opioid) was introduced. Any reported effect of opioids on breathlessness was captured after opioid doses were titrated to clinically effective doses. Opioids were routinely ceased if there was no reported improvement after dose titration. Opioid-related adverse events (reported by the patient or a carer, noted in any correspondence from the general practitioner or hospital admissions) were reviewed and documented during each clinic visit. Serious adverse events included accidental overdose, sedation, death and any adverse outcomes that required hospital admissions. Ethics approval for this study was provided by the Melbourne Health Human Research Ethics Committee (approval number: QA2020173).

Statistical analysis

Data are presented descriptively as counts with frequencies and summary statistics (including median values

Table 1 Patient demographics

Characteristic	Total ($n = 129$)	Opioids for breathlessness ($n = 109$)	Opioids for other indications ($n = 20$)	*P*-value
Age† (years)	76.1 (69.9–83.0)	77.6 (72.3–83.6)	68.6 (61.6–76.2)	<0.001*
Male	68 (52.7%)	57 (52.3%)	11 (55.0%)	0.824
Social situation				
Lives alone	27 (20.9%)	20 (18.3%)	7 (35.0%)	0.092
Local family or carers	121 (93.8%)	104 (95.4%)	17 (85.0%)	0.076
Resides in nursing home	22 (17.1%)	19 (17.4%)	3 (15.0%)	0.790
Smoking history				
Ex-smoker	91 (70.5%)	79 (72.5%)	12 (60.0%)	0.531
Active smoker	19 (14.7%)	15 (13.8%)	4 (20.0%)	
Primary respiratory diagnosis‡				
COPD	97 (75.2%)	80 (73.4%)	17 (85.0%)	0.922
Pulmonary fibrosis	23 (17.8%)	21 (19.3%)	2 (10.0%)	
Bronchiectasis	3 (2.3%)	2 (1.8%)	1 (5.0%)	
Other§	6 (4.7%)	6 (5.5%)	0	
Comorbidities				
Median number of comorbidities/patient†	7 (5.0–9.0)	6 (5.0–9.0)	8.5 (7.0–10.8)	0.008*
Co-existing lung cancer	4 (3.1%)	3 (2.8%)	1 (5.0%)	0.498
Anxiety	71 (55.0%)	59 (54.1%)	12 (60.0%)	0.628
Depression	53 (12.5%)	40 (36.3%)	13 (65.0%)	0.018*
Lung function†				
FEV_1% predicted	39.5 (29.0–55.3) ($n = 126$)	39.5 (29.8–56) ($n = 106$)	40 (24.3–50.5) ($n = 20$)	0.764
FVC% predicted	76.5 (62.8–88.0) ($n = 126$)	76 (61.8–88.8) ($n = 106$)	79 (67.5–87.8) ($n = 20$)	0.373
DLCO% predicted	32 (24.8–40.1) ($n = 118$)	31 (24.8–40.0) ($n = 98$)	35.5 (24.8–43.2) ($n = 20$)	0.317
6MWT distance (m)	40 (0–160.0) ($n = 128$)	30 (0–127.5) ($n = 108$)	120 (0–262.6) ($n = 20$)	0.052
PaO_2 (mmHg) on room air	53.9 (49.8–61.3) ($n = 94$)	54.1 (49.9–62.8) ($n = 83$)	52.6 (47.5–61.1) ($n = 11$)	0.767
$PaCO_2$ (mmHg) on room air	45.4 (39.3–51.7) ($n = 93$)	45.0 (39–51.9) ($n = 82$)	47.8 (41.8–51.0) ($n = 11$)	0.0.571
mMRC dyspnoea score				
1–2	7 (5.4%)	3 (2.8%)	4 (20.0%)	<0.001*
3	12 (9.3%)	7 (6.4%)	5 (25.0%)	
4	110 (85.3%)	99 (90.8%)	11 (55%)	

†Data are reported as counts with frequencies or medians with IQR.

‡Twelve patients with a primary diagnosis of non-COPD also had concomitant airway diseases (COPD or asthma).

§Including chronic thrombo-embolic disease, histiocytosis X, restrictive lung disease chest wall deformity and sarcoidosis.

*Significant value. 6MWT, 6-min walk test; age, at time of discharge, death or at the end of the data collection period (3 March 2020); COPD, chronic obstructive lung disease; DLCO, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range; mMRC, modified Medical Research Council.

with interquartile ranges (IQR) for skewed data). The Chi-squared test was used to compare proportions for categorical variables between patients taking opioids for breathlessness and those taking opioids for reasons other than breathlessness. The paired *t*-test was used to examine respiratory function and exacerbation frequency before and after opioid use. Mann–Whitney *U*-test was used to compare median values for non-parametric continuous data such as age, comorbidities, respiratory function, and opioid regimen between patients who were alive and deceased. Statistical significance was defined as $P < 0.05$. Data were analysed using IBM SPSS Statistics (version: 28).

Results

Between 1 April 2013 and 3 March 2020, 129 ALDS patients were prescribed opioids, of whom 68 (52.7%) were male with median age 76.1 (IQR = 69.9–83) years (Table 1). Three-quarters of patients had COPD as their

Table 2 Disease-directed management and outcomes ($n = 109$)

Management	*n* (%)
Non-pharmacological management	
Exacerbation action plan	71 (65.1)
Smoking cessation support for active smokers ($n = 15$)	15 (100)
Current or past pulmonary rehabilitation	95 (87.2)
Non-pharmacological breathlessness management education†	109 (100)
Respiratory physiotherapy	39 (35.8)
Domiciliary oxygen therapy	76 (70.3)
Pharmacological management	
LAMA inhaler(s)	88 (80.7)
LABA + ICS inhaler(s)	84 (77.1)
Up-to-date respiratory vaccines	103 (94.5)
Referral for advanced therapies	
Endobronchial valve insertion	6 (5.5)
Lung transplantation	4 (3.7)
Advanced care planning	
Discussed but no advance directive written	47 (43.1)
Advanced care directive completed	50 (45.9)
Goals of care documented during admissions	59 (54.1)
Palliative care support	
Palliative care consultant or registrar review in ALDS clinic	104 (95.4)
Community palliative care team support	60 (55.0)
Causes of death ($n = 81$)	
Respiratory cause	68 (84.0)
Non-respiratory causes	7 (8.6)
Not stated	6 (7.4)
Places of death ($n = 81$)	
Hospital palliative care unit	27 (33.3)
Hospital acute bed	18 (22.2)
Nursing home	13 (16.0)
Home	10 (12.3)
Community palliative care unit/hospice	8 (9.9)
Not stated	5 (6.2)

Data are reported as counts with frequencies.
†Including (but not limited to): breathing exercises, postures to reduce dyspnoea, activity pacing, energy conservation, fan therapy to face and breathlessness management plans. ALDS, advanced lung disease service; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist.

Table 3 Opioid management for breathlessness ($n = 109$ patients)

Opioid management	*n* (%)
Opioids for breathlessness commenced by	
ALDS	63 (57.8)
Inpatient respiratory team or other respiratory clinic	27 (24.7)
Palliative care team	7 (6.7)
GP	4 (3.8)
General medicine team	3 (2.9)
Not stated	5 (4.6)
Initial opioid regimen for breathlessness†	
Immediate release morphine only	37 (33.9)
Extended-release opioid regularly plus immediate release morphine as needed	17 (15.6)
Extended-release opioid daily	14 (12.8)
Extended-release opioid twice daily	6 (5.5)
Long-term opioid regimen for breathlessness†	
Extended-release opioid regularly plus immediate release morphine PRN	37 (33.9)
Immediate release morphine only	30 (27.5)
Extended-release opioids daily	22 (20.2)
Extended-release opioids BD	7 (6.4)
Opioid doses, median (IQR)‡	
Initial daily opioid dose consumed (OME) (mg)	5 (4.3–10)
Long-term daily opioid dose prescribed (OME) (mg)	12 (8–28)
Long-term daily opioid dose consumed (OME) (mg)	10 (5–18)
Opioid dose/regimen changed by	
Palliative care	12 (11)
GP	10 (9.2)
ALDS	7 (6.4)
Respiratory medicine	1 (0.9)
Side-effect	
Constipation	25 (23)
Sedation	4 (3.7)
Nausea	2 (1.8)
Hallucination	2 (1.8)
Dysphoria	2 (1.8)
Initial prescription of laxatives with opioid	49 (45)

†Data of initial opioid regimen was not available for 35 patients. Data of long-term opioid regimen was not available for 13 patients.
‡Data are reported as counts with frequencies or medians with IQR.
ALDS, advanced lung disease service; BD, twice daily; GP, general practitioner; IQR, interquartile range; OME, oral morphine equivalents.

primary respiratory diagnosis (96; 74.4%). Lung function was severely impaired with median predicted FEV_1 of 39.5% (IQR = 29.0–55.3%), severe hypoxemia at rest with median PaO_2 53.9 (IQR = 49.8–61.3) mmHg, and 122 (94.6%) patients had severe breathlessness with a mMRC dyspnoea score of 3 or 4 (out of 4). The median length of follow up (from first appointment to study census date or death) in the ALDS clinic was 18 (IQR = 8.4–35.3) months with a median of six (IQR 2.8–10.0) appointments per patient. There was no loss to follow up.

Twenty patients were prescribed opioids for indications other than breathlessness, of whom 17 patients used opioids for pain and three were previous intravenous drug users on a methadone programme. Patients taking opioids for breathlessness were significantly older ($P = 0.001$), had higher mMRC dyspnoea scores ($P < 0.001$) and significantly more comorbidities ($P = 0.008$), such as depression ($P = 0.018$), compared with patients taking opioids for other indications.

Table 4 Lung function tests before and during opioid treatment

Respiratory function test†	Before opioid treatment	On opioid treatment	*P*-value
FEV_1% predicted ($n = 38$)	37.6 (24.8–47.0)	35.4 (26.8–42.0)	0.111
FVC% predicted ($n = 38$)	83.3 (68.5–94.0)	81.4 (64.0–93.8)	0.384
DLCO% predicted ($n = 41$)	35.5 (26.5–44.0)	34.9 (26.0–42.5)	0.727
6MWT distance metres on air (m) ($n = 17$)	173.4 (65.0–260.0)	121.4 (60.0–135.7)	0.107
PaO_2 (mmHg) ($n = 17$)	56.0 (48.3–62.8)	52.5 (48.2–55.9)	0.129
$PaCO_2$ (mmHg) ($n = 20$)	47.0 (41.3–52.5)	49.1 (43.1–55.7)	0.086

†Data are reported as medians with IQR. 6MWT, 6-min walk test; ABG, arterial blood gas; DLCO, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 5 Opioid regimen and mortality ($n = 109$ patients)

Opioid use	Alive ($n = 28$)	Deceased ($n = 81$)	*P*-value
Length of opioid use for breathlessness (months)†	15.2 (2.5–49.6)	9.4 (2.9–22.2)	0.201
Long-term daily opioid dose prescribed (OME) (mg)†	11 (6.9–26.5)	12 (8–28)	0.575
Long-term daily opioid dose consumed (OME) (mg)†	5.5 (5–10)	10 (5–19.8)	0.130

†Data are reported as medians with interquartile ranges. OME, oral morphine equivalents.

Of the 109 (84.5%) patients who received opioids for breathlessness, 95 (87.2%) were either currently enrolled or had completed a pulmonary rehabilitation programme and 84 (77.1%) were prescribed inhaler therapy with any of long-acting beta-agonists, long-acting muscarinic antagonists and inhaled corticosteroid (Table 2). Non-pharmacological strategies to manage chronic breathlessness were discussed with all patients. Nearly all (104; 95.4%) patients saw a palliative medicine doctor in the ALDS clinic in addition to a respiratory physician. Eighty-one (74.3%) patients died over the study period.

Of the 109 patients who were prescribed opioids for breathlessness, 92 (84.4%) used opioids for breathlessness only and 17 (15.6%) for both breathlessness and pain. The median length of opioid use for breathlessness was 9.8 (IQR = 2.8–19.8) months. Two-thirds (69; 66.3%) of patients were commenced on opioids in the outpatient setting, with one-third (35; 32.1%) commenced during an inpatient admission by respiratory medicine (25; 22.95%), palliative care (7; 6.7%) or general medicine (3; 2.9%; Table 3). Opioids were initiated for over half (63; 57.8%) the patients by the ALDS team. Opioid medications regimens were individualised according to patient preferences, with the most commonly prescribed initial opioid medication being an immediate-release preparation (i.e. Ordine) used as required (37; 33.9%), and the most commonly prescribed long-term opioid regimen being an extended-release preparation (such as MS Contin or Kapanol) together with an immediate-release preparation as needed (37; 33.9%). The median opioid dose prescribed long-term for breathlessness was 12 (IQR = 8–28) mg oral morphine equivalents (OME)/day. Half (52.2%) of the patients reported being compliant with opioid treatment and most had no side-effects (61; 56%). Opioid therapy was ceased due to side-effects (such as constipation, dysphoria) in 12 patients and due to complete lack of efficacy in four patients (no effects on subjective breathlessness, self-reported walking distance, or other symptoms such as cough or pain). One patient stopped opioid therpy due to improvement in breathlessness. There were no major adverse events associated with opioid use.

Seventy-one (65.1%) patients reported a subjective improvement in breathlessness on opioid treatment; however, there was no significant change in the mean mMRC dyspnoea score on treatment ($P = 0.807$). Similarly, in the small number of patients who had matched lung function and arterial blood gas data available in the 3–18 months before and after opioid treatment was commenced, there was no significant change in lung function test measurements (Table 4). While the partial pressure of carbon dioxide increased slightly over time, this change was not clinically or statistically significant ($P = 0.086$). There was no association between mortality and the median length of opioid use ($P = 0.057$), or between mortality and opioid dose consumed ($P = 0.130$; Table 5).

Discussion

To our knowledge, this is the first Australian prospective cohort study to explore the real-world prescription and use of opioids for severe chronic breathlessness over several years in patients with advanced non-malignant respiratory diseases. The cohort included patients with poor respiratory function and multiple medical and psychological comorbidities, which is a group that is generally at increased risk from opioid associated adverse events.

Our study demonstrated that patients were willing to accept and compliant with low-dose opioid treatment for breathlessness, experienced subjective symptom improvement, and there were no serious adverse events.

Opioid regimens

Most clinical trials investigating the efficacy of opioids for severe chronic breathlessness have been of short duration (up to 1–4 weeks), with only one study adopting a longer follow-up period of 3 months.[28] Therefore, evidence regarding long-term benefits and harms in this patient population is lacking.

Low dose opioids were prescribed to ALDS patients only after disease-directed pharmacological therapy and non-pharmacological supportive approaches had been optimised. Immediate-release oral morphine was the most common regimen for opioid initiation, while a combined immediate-release and extended-release oral morphine regimen was most frequently prescribed long-term. Currently, the two recommended approaches for opioid initiation suggest either an immediate-release or extended-release oral morphine, with the latter being the most evidence-based regimen.[14,27,28,31,35] Nevertheless, a handful of studies have shown that physicians prefer to initiate small doses of immediate release oral morphine as their first choice, as this regimen permits lower doses and a more controlled gradual increase if required.[14,36–38] Furthermore, patients and carers are able to take time to observe opioid effects and accept opioid treatment, thus this approach may improve compliance.[23] While these approaches focus on individualising the opioid regimen according to patients' preferences and their abilities to safely use their medications, few guidelines offer specific recommendations regarding effective opioid regimens for chronic refractory breathlessness. Importantly, there is no evidence to support the prescription of multiple opioid preparations (both immediate and extended-release preparations) together for patients with chronic breathlessness, yet this approach was commonly adopted by different medical teams. This practice needs further investigation to understand if this was due to physicians adopting a similar management approach to pain, or driven by patients' unmet symptom needs when prescribed only extended-release morphine.

Opioid efficacy

More than half of the patients reported subjective reduction in the severity of breathlessness intensity and were compliant with opioid treatment; however, there was no change in the mMRC breathlessness scale (which was recorded at each clinic visit). It is worth noting that the mMRC scale is a unidimensional measurement of breathlessness (measuring only the effect of breathlessness on exercise capacity not breathlessness intensity, frequency or unpleasantness), with a limited number of grades (0–5). Furthermore, the scale is not time responsive, with little fluctuation.[39] Given the multidimensional nature of breathlessness including the sensory-perceptual, affective and impact domains,[26,40] a more comprehensive score such as the Dyspnoea-12 or Multidimension Dyspnoea Profile should be considered to capture the true long-term effects of opioids on breathlessness.[41–43]

Currently, it remains unclear which patients are most likely to benefit from opioids for severe chronic breathlessness. Johnson *et al*.[44] found that patients with worse baseline breathlessness were more likely to benefit from opioids. Those authors postulated that patients with worse symptoms might have more room for improvement.[44]

Studies regarding patients' perspectives have shown positive experiences with opioid treatment. Rocker *et al*. (2013) confirmed substantial and sustained self-reported opioid efficacy, where 27 (61%) of 44 COPD patients with chronic refractory breathlessness found opioids helpful at 4–6 months.[35] This was supported by the improvement in the numerical rating scale of breathlessness and chronic respiratory questionnaire. Furthermore, patients reported that 'small gains' in improving severe breathlessness had a 'big impact' on confidence, energy levels, mood, and relationships, which subsequently contributed to improved quality of life.[35] These positive effects were also reported by their family carers.[45] Therefore, opioids might offer at least some (if only slight) symptom relief for patients who have persisting breathlessness despite optimising disease-directed and non-pharmacological approaches.

Adverse events

There was no association between opioid use and change in lung function parameters or arterial blood gas parameters. These results are reassuring, given longstanding concerns that opioids may worsen respiratory failure in people with severe COPD.[37,46] However, this result should be interpreted with caution give the small number of patients with matched data before and after opioid initiation. Nevertheless, previous systematic reviews and meta-analyses examining the effects of opioids in people with severe breathlessness and advanced lung disease have similarly demonstrated that opioids do not have deleterious effects on arterial blood gas parameters.[29,30]

Our patients reported common opioid-associated side-effects that have been well described in previous clinical trials and systemic reviews, including constipation, sedation, nausea, hallucination and dysphoria.[27–31] As

gastrointestinal symptoms are common and may occur immediately after opioid use, laxatives and antiemetics have been recommended to use prophylactically with opioids.[47] In this study, laxatives were prescribed to just under half the participants. It is not clear if this represents a failure to prescribe prophylactic treatments or poor documentation, as these medications are usually bought over the counter (without prescription). Nevertheless, patients are more likely to benefit from and adhere to opioid treatment if symptom improvements outweigh side-effects,[45] therefore counselling and active anticipatory management of common side-effects are important.

No life-threatening or major adverse events were identified in our study despite the patient cohort being older with severe respiratory disease and significant comorbidities, and thus at increased risk of adverse events. Similarly, two past retrospective cohort studies examining opioid safety also reported a higher incidence of opioid use among elderly patients, frequent COPD exacerbators, and patients with lower functional status, increased CO_2 retention, and significant comorbidities.[48,49] Despite this patient population often receiving opioids, these patients are often excluded from the clinical trials. This highlights the importance of longitudinal, observational studies of real-world practice in providing critical data regarding both efficacy and patient safety.

Model of care

The ALDS is a comprehensive, integrated respiratory and palliative care service which aims to both optimise disease-directed care and offer a palliative approach to address unmet patients needs for complex physical, psychological and emotional issues.[34,50] More than half the patients (63, 57.8%) were commenced on opioids and monitored long term by the ALDS team. Nevertheless, a significant number of patients were first prescribed opioids for breathlessness as inpatients by various (non-ALDS) medical teams, despite past clinical trials focussing solely on outpatient opioid initiation[27,28,31] and evidence of major adverse events when opioids are commenced in the inpatient setting.[51] Almost all ALDS patients were referred to palliative care services and discussed advanced care planning. Models of care similar to the ALDS have also been introduced in the UK and Canada and shown to have benefits on symptom management, patients' quality of life and burden of healthcare costs.[52–55]

Strengths and limitations

This is the first Australian, prospective cohort study to examine the real-world prescription of opioids for chronic breathlessness over several years. The strengths of this study lie in the relatively large sample size and broad patient population with chronic respiratory conditions and severe refractory breathlessness.

This was a single-centre study and the model of care delivered by the ALDS is unique, therefore the findings may not be representative of other clinical environments. The lack of data from the primary care setting is recognised. The quality of documentation in patients' clinical notes and the ALDS database was high with complete data available for most patients. Quality of life was not formally measured during routine clinic visits. Similarly, few patients underwent lung function tests (due to the burden of testing on the patient) after an opioid was commenced. Therefore, the study lacked power to examine associations between opioid use and temporal lung function change. Further research is needed to determine the long-term effects of opioids on quality of life and lung function parameters in this patient population.

Conclusion

Patients with advanced, non-malignant lung diseases and severe chronic breathlessness reported a subjective beneficial effect from low dose opioids on breathlessness and continued to use opioids over many months, without serious adverse effects. Ensuring patients receive individualised care, opioid education, support and follow up is important to mitigate risks in this older patient group, who are more vulnerable to adverse events.

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