Ethical approval: MEC approval was given by METC azM/UM Maastricht, The Netherlands, Dec 6, 2017, number NL62110.068.17/METC172020.

This study was registered at EudraCT, number 2017-002192-25.

Data are available at request (corresponding author).

There are no conflicts of interest to report.

References

1. Ashby M, Fleming B, Wood M, Somogyi A. Plasma morphine and glucuronide (M3G and M6G) concentrations in hospice inpatients. J Pain Symptom Manage 1997;14:157–167.

2. Lalovic B, Kharasch E, Hoffer C, et al. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. Clin Pharmacol Ther 2006;79:461–479.

3. Masman AD, Tibboel D, Baar FP, et al. Prevalence and implications of abnormal laboratory results in patients in the terminal phase of life. J Palliat Med 2016;19:822–829.

A Randomized, Double-Blind, Multisite, Pilot, Placebo-Controlled Trial of Regular, Low-Dose Morphine on Outcomes of Pulmonary Rehabilitation in COPD

To the Editor

To date, opioids have not been shown to improve respiratory measures such as the six-minute walk test in the short term.[1] In the longer term, regular, low-dose opioids have been shown to reduce the intensity of chronic breathlessness.[2]

Fear of breathlessness is one factor that can deter people from participating in pulmonary rehabilitation, especially in people with more severe chronic obstructive pulmonary disease (COPD).[3] The hypothesis was that if day-to-day exertion could be increased before breathlessness supervened during the whole course of pulmonary rehabilitation by the use of regular, low-dose, sustained-release morphine, then patients' outcomes may improve to a greater degree.[4,5] This pilot study sought to understand the feasibility of recruitment to such an adequately powered Phase III study.

This early phase study was a multisite, double-blind, fixed-dose, randomized placebo-controlled trial of regular, low-dose sustained-release morphine. This was an early phase study with a priori stop/go parameters including the following: the feasibility of recruitment to the protocol, acceptability to clinicians and participants, and the signal of any difference between arms on which to base the sample size calculation for a definitive study and improve the measurable success of pulmonary rehabilitation in people with COPD and moderate-to-severe breathlessness at baseline.

It was conducted in three large university teaching hospital pulmonary rehabilitation outpatient programs in two states of Australia.

The following clinical eligibility criteria were included: adults (age ≥18 years) eligible for pulmonary rehabilitation and enrolled in the eight-week course; with moderate (40%–60% predicted FEV_1) or severe COPD (<40% predicted FEV_1)[6]; breathlessness score of 3 or 4 on the modified Medical Research Council (mMRC) breathlessness scale[7]; and on stable medications for breathlessness over the prior week except routine "as needed" medications.

The intervention was 20 mg mane of regular, sustained-release morphine (matched with blinded docusate with sennosides A and B) and the control was placebo morphine (matched with placebo laxative) for the eight weeks of outpatient pulmonary rehabilitation. All participants had access to open-label docusate with sennosides as needed.

The proposed outcome for the Phase III was change in 6 MW distance at eight weeks from baseline.[8] Elements for feasibility included recruitment and retention rates, safety, acceptability, and evaluation of the outcome measures (efficacy of the intervention, measurability, and variance). The first stop/go outcome was recruitment. It was hoped to recruit 20 people in the 12 months of the study in one site.

The study was registered before commencement and approved by all relevant Human Research Ethics Committees. All participants provided written informed consent. The study was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR): 12615000121561.

A total of 1143 people were referred to pulmonary rehabilitation in the three sites during which the study was open. In total, only nine people were randomized in 18 months, of whom six completed the study.

The major reason for screen failure was the criterion for people to have an mMRC of 3 or 4. People referred to pulmonary rehabilitation in this study had mMRC scores of 1 or 2 almost entirely—people in these pulmonary rehabilitation services were universally ineligible because they did not meet the mMRC criteria. Safety, acceptability, and measures for the outcome of a definitive study could not be undertaken given the failure to recruit.

This study was conducted in large, research-active pulmonary rehabilitation services. The rate of recruitment was not adequate to justify further investment in this early phase study and negated any further planning for a phase III study. People with Level 3 or 4 mMRC breathlessness were (systematically) not referred to pulmonary rehabilitation.

GOLD 2019 guidelines recommend that pulmonary rehabilitation is one of the most cost-effective

treatment strategies for people with COPD and should be an integral part of management for chronic breathlessness.[9,10] There is objective evidence that people with mMRC 3 or 4 will derive clinically relevant benefit,[10] but such benefit can only be realized if people are referred. The results of our study challenge a key GOLD eligibility criterion for referral to pulmonary rehabilitation: if a person is breathless with COPD, they should be referred to pulmonary rehabilitation no matter how severe their disease or its symptoms. Our study shows that people with moderate-to-severe chronic breathlessness do not seem to be referred to pulmonary rehabilitation. This is an important finding that adds to the known barriers to referral to pulmonary rehabilitation by primary care physicians that include lack of belief in the benefits of pulmonary rehabilitation for COPD in general, logistical difficulties (such as workload and limited time), and "ownership" of the guidelines' content.[11]

Barriers to service access in large hospital sites include the challenge of using public transport to attend pulmonary rehabilitation or parking on the site often with long distances to walk to the clinical areas. This creates a self-selection process that only reasonably fit and well people can attend pulmonary rehabilitation in these settings.

Tertiary hospital pulmonary rehabilitation in real-world practice does not seem to be the first step for managing severe chronic breathlessness despite international guidelines. This may differ from community-based pulmonary rehabilitation where some of the physical barriers may be lessened. We need to understand how current eligibility criteria for pulmonary rehabilitation are actually operationalized and identify systematically people who may be missing out.

This also raises the question as to whether a pulmonary rehabilitation program that focuses on people with the most severe breathlessness should be implemented and evaluated, aiming to help them maintain their current functional status for longer, even if function cannot be improved.

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References

1. Ekström M, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. BMJ 2014;348:g445.

2. Ekström M, Bajwah S, Bland JM, et al. One evidence base; three stories: do opioids relieve chronic breathlessness? Thorax 2018;73:88–90.

3. Harris D, Hayter M, Allender S. Improving the uptake of pulmonary rehabilitation in patients with COPD: qualitative study of experiences and attitudes. Br J Gen Pract 2008;58:703–710.

4. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2012;380:2095–2128.

5. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006;CD003793.

6. Yang IA, Brown JL, George J, et al. COPD-X Australian and New Zealand guidelines for the diagnosis and management of chronic obstructive pulmonary disease: 2017 update. Med J Aust 2017;207:436–442.

7. Bestall JC, Paul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54:581–586.

8. Chandra D, Wise RA, Kulkarni HS, et al. Optimizing the 6-min walk test as a measure of exercise capacity in COPD. Chest 2012;142:1545–1552.

9. 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (an update on GOLD 2017). Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf. Accessed June 1, 2019.

10. Evans RA, Singh SJ, Collier R, Williams JE, Morgan MD. Pulmonary rehabilitation is successful for COPD irrespective of MRC dyspnoea grade. Respir Med 2009;103:1070–1075.

11. Johnston K, Grimmer-Somers K. Pulmonary rehabilitation: overwhelming evidence but lost in translation? Physiother Can 2010;62:368–373.

Parent Perspective and Response to Challenges and Priorities for Pediatric Palliative Care Research

To the Editor:

We write to express our appreciation for the many tributaries of care and concern around pediatric palliative care research that are reflected in the article **Challenges and Priorities for Pediatric Palliative Care Research** (Feudtner et al.[1]). We are caregivers whose children and families have been the beneficiaries of pediatric palliative care, and we are dedicated to building awareness of its critical value in our roles as staff and parent members of the Courageous Parents Network, a national nonprofit organization whose mission it is to empower, orient, and support parents caring for children with serious illness. We are greatly encouraged by the breadth of issues and depth of understanding evidenced in this article. We are delighted that these distinguished investigators are expressing interest and enthusiasm for pursuing collaboration and direction of resource, and we envision endless benefit.

While there are times and places for many different voices, our group noted that the panel participating in this study was lacking *our* voices. The involved providers clearly have deep expertise and know our population well. We believe, however, that there is no real substitute or proxy for actual family experience.

Going a step further, we can state with confidence that where our providers have encouraged our input and relied on our knowledge of our children, all parties have found greater satisfaction with the care process—no matter how sad the ultimate outcome is. *Families* can *bring this knowledge and experience to the research agenda.* Families could be a part of the research design, not just as subjects but also as investigators. The work of the Patient-Centered Outcomes Research Institute is a good model for this.

In the meantime, how can what matters for the advancement of the field and the academic advancement of the individual researchers be effectively married with what matters to families?

In the spirit of mutual understanding, we brainstormed needs and desires and offer this prioritization from the list in the article.

1. Communication and facilitating goals-of-care clarification and decision-making: In our experience, pediatric palliative care providers own this space—it is the unique domain of pediatric palliative care. Other specialists may or may not be trained to pursue the family's goals of care or to have the long view of the patient's and family's priorities. And yet, having the ability to at least initiate important conversations on these topics is critical to the family's well-being. We suggest—no, hope—that investigation and publication of best practices would travel upstream, that is, to equip providers in all related fields, and at all levels, with tools to support safe and candid communication.
2. Improve symptom management and quality-of-life interventions: While we designated this as our second priority, symptom management and related interventions are, in fact, inextricably linked to goals of care (previous point) and family impact (the next point). A child's pain, for example, affects the entire family. When the child suffers, the parents' ability to think clearly and rationally, to communicate with each other and with the care team, and even to care for other children in the family can all be severely compromised. Ideally, the burden of symptom management would be left to other specialists. However, the fact is that palliative care specialists take into account the whole child in ways that specialists may miss. Anything and everything that improves this practice is relevant to the most important role of pediatric palliative care: stewardship of the child and family's quality of