



Is being able to walk to the letterbox life-changing? A qualitative assessment of measures of improvement in persistent breathlessness

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To the Editor:

Persistent breathlessness is a prevalent cause of disability in COPD [1]. Many people with COPD do not achieve acceptable symptom control despite optimisation of disease-specific and nonpharmacological treatments [2]. Regular, low-dose, sustained-release morphine may reduce persistent breathlessness in some people, noting wide interindividual variation in benefits and harms. Ideally, sustained-release morphine should only be prescribed to people who are likely to experience a net benefit. To date, the clinicodemographic characteristics of people most likely to benefit from sustained-release morphine for persistent breathlessness have not been defined. Benefits quantified need to reflect people's perceptions [3].

This study aimed to explore how experiences of large perceived qualitative benefits from regular, low-dose, sustained-release morphine for persistent breathlessness may be reflected in changes in clinical, quantitative measures of efficacy and safety.

This was an exploratory analysis of qualitative and quantitative data from a phase III, double-blind, dose-increment, randomised, placebo-controlled trial (RCT) of regular, low-dose, sustained-release morphine for persistent breathlessness [4]. The trial and the qualitative substudy were approved by the Hunter New England Human Research Ethics Committee (ref. 15/12/16/3.06).

Participants had COPD and a modified Medical Research Council (mMRC) breathlessness scale score ≥ 3 at baseline despite optimal treatment of the underlying disease(s) [4]. The study included three sequential randomisations (weeks 1, 2 and 3) to final doses of sustained-release morphine (0 (*i.e.* placebo), 8, 16, 24 or 32 mg). There was an optional 6-month blinded extension using the dose prescribed in week 3. 13 patients and, separately, their caregivers were interviewed about their experiences of persistent breathlessness before and after initiating the study medication as part of a pre-planned qualitative study [5]. Interviews were conducted at participants' homes, while the participants and interviewer were still blinded. Quotes were taken directly from participants' transcripts.

Two participants used the term "life-changing" to describe their experiences with the study medication and were identified as "super-responders" (both on sustained-release morphine). None had psychological comorbidities (Hospital Anxiety and Depression Scale score ≤ 7 for both anxiety and depression). Quantitative measures obtained in the RCT were explored for changes meaningful to participants including: breathlessness and functional impairment due to breathlessness (0–10 Numerical Rating Scale (NRS), mMRC, Chronic Respiratory Disease Questionnaire (CRQ) – dyspnoea and mastery); activity measures collected from FitBits; performance status (Australia-modified Karnofsky performance status (AKPS)); quality of life (EQ-5D-5L questionnaire); perceived sleep quality and daytime sleepiness (Leeds Sleep Questionnaire and Epworth Sleepiness Scale); harms (constipation, nausea and drowsiness); global impression of change (GIC) (7-point Likert scale); and caregiver's burden (Zarit Burden Interview (ZBI-12)).

Super-responders' final doses of morphine were 16 and 24 mg, and both continued in the 6-month blinded extension. Neither had unplanned hospital presentations throughout the study. Participant 1 highlighted, "Climbing a set of stairs was difficult. There were steps up from [location A] to [location B], three



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flights... I would try going up those, but it took at least three stops to get from the bottom to the top, and then I was panting... [...] About a month ago I walked up all three flights and continued walking without a pause. And that is more or less across the board. I can do things now that I haven't been able to do for a long, long time."

Participant 2 emphasised, "Breathing became easier. [...] I used to battle to walk down to the letter box and back. Now I can walk down to the letter box with no problem. It has improved to that degree."

Quantitatively, functional changes reported by participants were accompanied by reductions in mMRC and CRQ-dyspnoea scores, and an improvement in GIC (table 1). The number of active minutes and active calories (*i.e.* triggered by activity of ≥ 10 min, burning three times as many calories as those spent at rest) improved in both participants. After 6 months of sustained-release morphine, these quantitative improvements persisted.

Participant 1 experienced a reduction in the breathlessness NRS intensity scores (*i.e.* "worst" and "average" breathlessness in the previous 24 h), and an improvement in CRQ-mastery, AKPS and EQ-5D-5L scores. These were mostly unchanged for participant 2. Daily steps and daily calories were relatively stable (participant 1) or decreased (participant 2).

Both participants reported better sleep and higher energy levels during the day. Participant 1 said: "My wife particularly noticed a significant increase, I would say within a week, with my energy levels, my ability to hyper exertion without gasping. I think you also notice a difference in my breathing at night that I was not gasping. I had been subjected to significant coughing fits on a regular basis. This came down to almost to nil. And there is a feeling of wellbeing."

Participant 2 reported: "[Before taking morphine] I'd wake up probably a couple of times a night to go to the toilet and then when I come back from the toilet it takes me a while to go back to sleep because of the breathing. [...] [After taking morphine] Breathing became easier, I slept quite a lot more you know? I go to bed at 10 o'clock at night and sleep until 8:00 am in the morning. Quite honestly, I don't think I could manage without it [morphine]."

Most quantitative measures of perceived sleep quality improved consistently throughout the study, except for daytime sleepiness (increased for participant 1).

Constipation was the only harm reported in the first few days of therapy, which required adjustment of the participants' medication or trying new interventions. However, the participants never considered stopping the study medication because the perceived benefits outweighed perceived harms, findings reflected in quantitative assessments. Participant 1 reported: "Constipation was the downside and that was really the only downside. They give you the pills [laxatives] but they should issue bottles of prune juice because they would be a lot more effective."

Participant 2 said: "Constipation is also a problem with the drug [morphine]. And it wasn't anything that you couldn't adapt to. [...] So OK, you mightn't go to the toilet twice a day and use your bowels and you might miss a day. But it does not matter, you know?"

At interview, caregiver 1 reported: "My life changed. I am not worried every minute of every day; I don't sit up in bed and listen to him breathing. And we can go out and enjoy life more." Caregiver 2 reported not being involved in hands-on care, living her life fairly detached from the patient. These experiences translated into a significant reduction in the ZBI-12 score for caregiver 1, sustained for 6 months. The absence of burden for caregiver 2 was reflected in the ZBI-12.

This analysis explored the relationship between subjective qualitative experiences of breathlessness and changes in multiple quantitative measures of benefits and harms, while sustained-release morphine was being introduced and continued in two men with COPD. The results suggest functional improvement is a key driver of perceived benefit, which seems to be accompanied by clinically meaningful reductions in CRQ-dyspnoea [6], appreciable improvements in mMRC scores and an increase in active steps per day.

Compared to participants reporting small or no benefit, super-responders reported that they could perform more meaningful activities [5]. More importantly, they actually engaged in such activities, which is not always the case for people who increase their functional capacity [7]. Possibly, a quick functional adjustment to a new threshold of breathlessness is one of the key characteristics of super-responders.

TABLE 1 Daily doses of sustained-release morphine and quantitative study measures across study stages for the two super-responders identified through the semistructured interviews

	Participant 1 [#]				Participant 2 [†]			
	Baseline	Week 1	Week 3	6 months	Baseline	Week 1	Week 3	6 months
SR morphine daily dose, mg		16	16	16		8	24	24
NRS breathlessness, 0–10 points								
Worst	6.5	3.7	0.3	1	5	6	6.6	6
Average	3	3.3	0.3	1	3.5	3.6	4.3	4
Unpleasantness	6	2.3	0	1	2	1	1	1
mMRC	3	3	1		3	2	2	
CRQ								
Dyspnoea	4.25	5.4		6	2.8	5		5
Mastery	4	6.25		6.25	5.75	5.75		5.75
FitBit data[‡], average per day								
Caloric expenditure, kcal	2390.0	2404.3	2492.0		1969.0	1742.3	1933.7	
Number of steps (distance, km)	5365 (3.9)	4118 (3.0)	5447 (4.0)		1007 (0.7)	975 (0.7)	406. (0.3)	
Time spent sedentary, min	1192.5	1219.7	1045.0		1440.0	745.0	1245.3	
Time spent lightly active, min	192.0	146.3	192.0		0.0	42.7	25.0	
Time spent fairly active, min	9.5	39.3	18.7		0.0	0.0	0.0	
Time spent very active, min	0.0	7.0	8.0		0.0	0.0	0.0	
Caloric expenditure with activity, kcal	854.0	879.0	1006.3		0.0	159.7	100.0	
AKPS	70	70	90	80	60	60	60	60
EQ-5D-5L VAS	57	75		60	60	60		65
Sleep measures								
“How well did you sleep last night?”	Poorly	Moderately well	Moderately well	Moderately well	Moderately well	Very well	Very well	Very well
Epworth Sleepiness Scale	11	11		13	2	7		3
Leeds Sleep Questionnaire								
Getting to sleep	31.3	55.0		48.0	47.0	50.0		77.3
Quality of sleep	40.5	65.0		49.5	48.0	51.0		64.0
Waking in morning	50.5	58.0		58.0	47.0	52.0		36.0
Behaviour following waking	72.0	63.7		55.3	50.7	53.3		51.3
Constipation	Not at all	Severe	Not at all	Not at all	Not at all	Moderate	Mild	Mild
Global impression of change		Minimally improved	Very much improved	Very much improved		Much improved	Minimally improved	Much improved
	Caregiver for participant 1				Caregiver for participant 2			
	Baseline	Week 1	Week 3	6 months	Baseline	Week 1	Week 3	6 months
ZBI-12, 0–48 points	29	26	6	12	0	0	0	0

SR: sustained-release; NRS: Numerical Rating Scale; mMRC: modified Medical Research Council scale; CRQ: Chronic Respiratory Disease Questionnaire; AKPS: Australian Karnofsky Performance Status; VAS: visual analogue scale; ZBI-12: Zarit Burden Interview. [#]: participant 1 was participant 2 in the qualitative study previously published [5]. [†]: participant 2 was participant 6 in the qualitative study previously published [5]. [‡]: baseline values are mean scores across 2 days; week 1 and 3 values are mean scores of the last 3 days of each week (corresponding to morphine steady-state plasma concentrations).

Super-responders may also be less vulnerable to anticipatory anxiety before breathlessness-inducing activities, as suggested by low baseline anxiety scores. Adjustments to new levels of physical activity are unlikely to be translated into changes in unidimensional breathlessness measures but may be captured by appropriate assessment tools covering function [8, 9].

The daily number of active minutes and active calories seem to better reflect perceived changes in function, compared to number of calories or number of daily steps. Possibly, super-responders are strategic in engaging in daily activities that are meaningful to them and that were previously out of scope. Even small gains in function create a greater sense of worth and wellbeing [10]. These moments of targeted and calculated exertion are unlikely to be captured by the total number of daily steps but may be reflected in measures of more strenuous activity.

People with persistent breathlessness report better subjective sleep quality after initiating sustained-release morphine [11]. This study suggests that subjective sleep improvements may be critical to improve people's perceived energy levels during the following day and, perhaps, facilitate functional gains. Better subjective sleep quality for patients may also translate into decreased burden for caregivers, for whom breathlessness is distressing to witness (including during the night) [12].

Gains in function outweighed the transient harms of constipation, despite its troubling nature. Prevention and ongoing management of constipation is important to achieve a net benefit from sustained-release morphine [3].

This study may have a critical role in informing the design of large-scale studies assessing value-based therapy for people with persistent breathlessness and their caregivers, in which self-reporting measures ought to be central [13]. It is not intended that these results be generalised but that they inform a discussion of outcomes that should be used subsequently. While symptom reduction needs to be a priority in the short term, it is critical to ensure patients remain physically active in the medium-to-long term, which may reduce deconditioning and social isolation.

Future research needs to focus on identifying the best outcome measures for people with persistent breathlessness, which may include the use of multidimensional assessment tools [14] and measures of daily function. In particular, the daily numbers of active minutes and active calories need to be investigated as primary outcome measures in future studies.

In conclusion, perceived improvements in meaningful activity and sleep may be key drivers of benefit for patients with persistent breathlessness and their caregivers. The best outcome measures for these populations need to be investigated in future qualitative and quantitative studies.

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