

# Patients' and their caregivers' experiences with regular, low-dose, sustained-release morphine for chronic breathlessness associated with COPD: a qualitative study

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## ABSTRACT

**Introduction** Regular, low-dose, sustained-release morphine is effective in reducing chronic breathlessness in people with advanced disease, particularly in patients with chronic obstructive pulmonary disease (COPD). Despite experiencing a reduction in breathlessness, some patients choose not to continue long-term treatment.

**Aim** This study aimed to explore patients' and caregivers' experiences with regular, low-dose, sustained-release morphine for chronic breathlessness associated with COPD.

**Methods** A qualitative study embedded in a randomised controlled trial (RCT) of regular low-dose, sustained-release morphine for chronic breathlessness for people with COPD and modified Medical Research Council breathlessness scale 3–4. After completing the RCT or withdrawing, patients and their caregivers were invited to participate in interviews in their homes focused on their experiences with the trial medication while still blinded to the arm to which they had been allocated. Data analysis used a constant comparative method informed by the principles of grounded theory.

**Results** Thirteen patients and nine caregivers participated. Four themes were identified: (1) Receptivity and knowledge; (2) Function as a priority; (3) Harmful and helpful side effects; and (4) Therapy-centred aspects. The concept of 'net effect' emerged from the interplay between themes, subthemes and the decision to continue taking sustained-release morphine during the trial and after trial completion.

**Conclusion** Clinicians' support and preconceived ideas about morphine influence the decision to commence sustained-release morphine. The hope for functional improvement is the great driver influencing positively the decision to take sustained-release morphine in the long term. The degree of symptom reduction, improved function, side-effects' severity and caregivers' availability creates a net effect driving patients' decisions to continue or discontinue the medication.

## INTRODUCTION

Chronic breathlessness is a clinical syndrome consisting of disabling breathlessness despite

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite experiencing a reduction in breathlessness with regular, low-dose, sustained-release morphine, some people choose not to continue this medication in the long term.

## WHAT THIS STUDY ADDS

⇒ This study suggests that functional improvement, rather than symptomatic improvement, is the greatest driver influencing positively the decision to take regular, low-dose, sustained-release oral morphine in the long term.

⇒ The concept of net effect helps to understand what motivates people to continue therapy with sustained-release morphine for chronic breathlessness.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ This study highlights therapeutic outcomes that are important for people with chronic breathlessness associated with chronic obstructive pulmonary disease, which need to be considered both in the clinical and research settings.

optimal treatment of the underlying condition(s).<sup>1</sup> As the prevalence of chronic respiratory diseases increases,<sup>2</sup> chronic breathlessness is also expected to increase leading more patients to experience severe functional limitations,<sup>3</sup> social isolation,<sup>4</sup> lower quality of life<sup>5</sup> and increased mortality.<sup>6,7</sup> Additionally, chronic breathlessness affects basic human needs, including independence<sup>8</sup> and sexuality.<sup>9</sup>

Caregivers are often the only source of support for people with chronic breathlessness, providing help with daily activities and emotional functioning.<sup>10,11</sup> Additionally, caregivers are often overburdened by the person's breathlessness, experiencing a constant state of hypervigilance and concern about the

patient's health, while also feeling restricted in their daily lives and trapped in the caregiver's role.<sup>10</sup> Caregivers have a central role in breathlessness management, and are uniquely positioned to provide feedback on the benefits and harms from treatments for the symptom.<sup>12</sup> Therefore, understanding both patients' and caregivers' experiences with any symptomatic intervention is pivotal.

Chronic breathlessness management involves optimising treatment for the underlying cause(s), and non-pharmacological and pharmacological approaches.<sup>13 14</sup> Morphine is the only pharmacological therapy for chronic breathlessness recommended by national and international guidelines.<sup>15 16</sup> Specifically, the use of regular, low-dose, sustained-release morphine for chronic breathlessness<sup>17–19</sup> has recently been approved by Australian regulatory bodies in doses of 10–30 mg a day.<sup>20</sup> However, one in three patients do not experience a reduction in breathlessness<sup>18</sup> with these doses and those who achieve symptomatic benefit, do not always choose to continue therapy in the long term.<sup>21</sup>

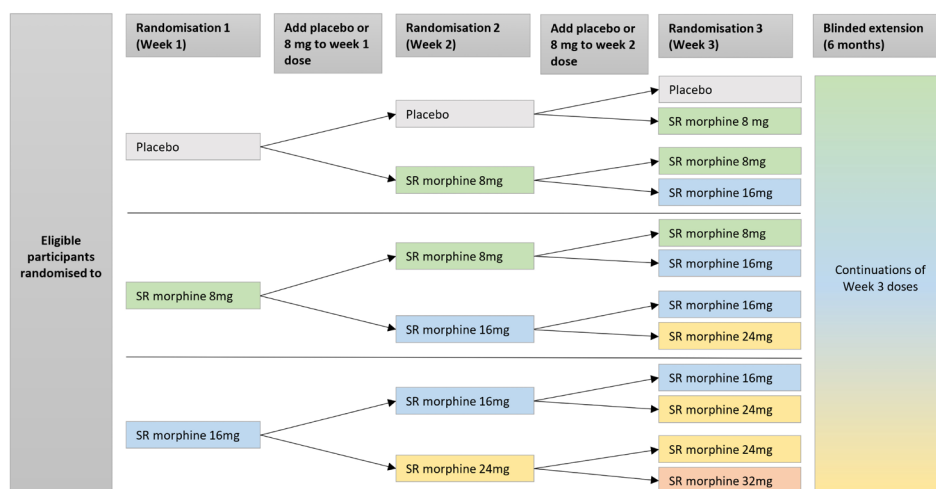
People's adherence to any therapy is influenced by: patient factors (eg, beliefs, self-efficacy); treatment-related factors (eg, administration method, dose, side-effects); and social factors (eg, patient-prescriber relationship, patient-caregiver relationship, social support).<sup>22</sup> Understanding causes of adherence/non-adherence in people with chronic breathlessness taking regular, low-dose, sustained-release morphine, necessarily means giving voice to those who experience this therapy first-hand (ie, patients and caregivers). Previous qualitative work suggests that patients and caregivers find opioids to be helpful for breathlessness and improve quality of life.<sup>23</sup> However, such work included different opioids and formulations, and focused exclusively on patients who were already successfully taking regular prescribed opioids (and potentially having benefit). By contrast, this study sought the views of patients and caregivers as therapy was introduced.<sup>18 20</sup>

This qualitative study aimed to explore patients' and caregivers' experiences with regular, low-dose, sustained-release morphine for severe chronic breathlessness associated with chronic obstructive pulmonary disease (COPD), whether they had benefit or not. The aim was to understand factors influencing patients' decision to continue this medication.

## METHODS

### Study design

An optional qualitative study embedded in an multicentre, phase III, effectiveness, randomised, placebo-controlled (RCT) trial with a parallel-arm, dose-increment design, evaluating regular, low-dose, sustained-release morphine for severe chronic breathlessness associated with COPD (Breathlessness Exertion And Morphine Sulfate (BEAMS) Trial).<sup>24</sup> Effectiveness studies ensure that participants included reflect the population of interest as closely as possible.<sup>25 26</sup> Participants were initially randomised to one of three arms: placebo, 8 mg or 16 mg of once-daily sustained-release morphine for 7 days. In weeks 2 and 3 there were two additional randomisations, which added either placebo or sustained-release morphine 8 mg to the previous dose. At the end of the 3-week randomisation period, morphine doses were 0 mg (ie, placebo), 8 mg, 16 mg, 24 mg or 32 mg, with 1:12 chance of being on placebo (figure 1). The study also offered an optional 6 months blinded extension in which participants continued taking the dose offered on week 3. All participants took blinded laxatives to prevent constipation and additional open-label laxatives as needed. The BEAMS Trial included an additional seven optional substudies to which participants were also invited. Participants were encouraged to select a maximum of one or two substudies in which to participate so as to prevent overburden and facilitate study completion.



**Figure 1** Design of the Breathlessness Exertion And Morphine Sulfate (BEAMS) multi-site, double blind, placebo controlled randomised trial of regular, low-dose, sustained release morphine for the symptomatic reduction of chronic breathlessness in people with chronic obstructive pulmonary disease (COPD). SR, Sustained Release.

After ceasing the study intervention, participants were invited to an interview about their (1) Experiences of living with breathlessness before the trial; and (2) Experiences with the trial medication (ie, placebo or morphine). This study reports these experiences with trial medication only. The study is reported using the Consolidated criteria for Reporting Qualitative research framework.<sup>27</sup> The research team included experts in chronic breathlessness (DF, DC), patient-centred research designs (AH, JP), linguistics (SK), qualitative enquiry (JP) and palliative care (JP, DC).

### Patient and public involvement

The study design and topic guides were informed by: (1) Previous quantitative work in a similar setting<sup>23</sup> (2) Factors known to be relevant for patients' choices related to therapy, and (3) Informal discussions with patients and caregivers prior to study initiation.<sup>22</sup> During the development of topic guides, the research team received continuous feedback from experienced clinicians/researchers who were seeing people with COPD-associated breathlessness (online supplemental appendix 1). While the study was being conducted, the topic guide was continuously adjusted based on themes emerging from participant responses.

### Participants

Participants were recruited from the Southern Adelaide Palliative Services, serving a metropolitan region in Adelaide, Australia. Convenience sampling was used to recruit participants who had concluded their participation in the BEAMS Trial (ie, completion or withdrawal)<sup>24</sup> between July 2017 and November 2018. Patients had COPD and a modified Medical Research Council (mMRC) breathlessness score of 3 or 4 corresponding to 'stops for breath after walking about 100 metres or stops after a few minutes walking on the level' and 'too breathlessness to leave the house or breathlessness when dressing or undressing'.<sup>28</sup> Caregivers, defined as 'the person who is closest to the patient',<sup>29</sup> were invited to participate, if available. Potential participants were first identified and contacted (ie, face-to-face or by phone) by the trial nurses. Those who agreed to participate in the qualitative substudy were then telephoned by the interviewer for the first time. In a subsequent face-to-face meeting, the interviewer explained the reasons for conducting the study, detailed the study procedures and clarified participants' questions before obtaining written informed consent.

### Data collection

General demographics were obtained for all participants. DF (female, medical doctor, full-time doctoral student trained in qualitative methodologies) conducted face-to-face, semistructured interviews with patients and caregivers separately, creating a safe and private

environment where participants could express their concerns.<sup>30</sup> Interviews were conducted at participants' home. No one else was present in the interview room. Interviews were audio-recorded and transcribed verbatim. Field notes were collected during each interview and the interviewer kept a reflective journal with impressions from each participant-researcher encounter. To minimise burden in this frail population, participants were only contacted a second time if the researchers overseeing the transcription (DF, AH) disagreed or had any doubts regarding what they have said.<sup>31</sup> Data collection continued until reaching saturation, as determined by discussion between researchers (DF, JP, DC).

### Unblinding

Participants and researchers were still blinded during interviews. Unblinding was carefully planned to avoid compromising the trial's integrity, which was still open to recruitment. Once data collection was completed, researchers without direct clinical care responsibilities were selectively unblinded to participants' allocated arms for people in the qualitative study only. All participants had finished their participation in the trial. Allocations were not disclosed to other participants or study staff.

### Analysis

Data analysis was conducted (NVivo Mac; V.11.4.0) following principles of grounded theory,<sup>32</sup> using a constant comparative approach.<sup>33 34</sup> Interview transcripts were open-coded (DF, AH); codes were grouped into themes (DF); and each theme was attributed different quotes to confirm coding validity (DF, JP). Concepts emerging from the patients' and caregivers' data were then compared and contrasted.

### RESULTS

Fifteen patients and 11 caregivers were invited to participate. Two patients declined participation citing fatigue and their caregivers were excluded. Thirteen patients and nine caregivers were interviewed. Interviews took up to 55 min to complete. Nine patients were male, with a median age of 76 years (IQR 68–78), who were severely limited by breathlessness but still able to function outside their homes (mMRC 3 (n=13)). More patients required some degree of assistance on a daily basis (Australian-modified Karnofsky Performance Status ≤60 (n=9)). Six caregivers were women, and patients' spouses (median age 70 years (IQR 69–79)). Most caregivers lived with the patients spending a large proportion of their time together (table 1).

Eleven patients took sustained-release morphine during the study (table 2): 8 mg (n=4); 16 mg (n=3); 24 mg (n=3); and 32 mg (n=1). Four themes described the combined experience of patients and caregivers: (1) Receptivity and knowledge (2) Function as a priority; (3) Harmful and helpful side effects; and (4) Therapy-centred aspects

**Table 1** Participants' characteristics in a qualitative substudy embedded in a multisite, double-blind, placebo-controlled randomised study of regular, low-dose, sustained release morphine for the symptomatic reduction of chronic breathlessness in people with chronic obstructive pulmonary disease (COPD)

	Patients (n=13)	Caregivers (n=9)
Median age, years (IQR)	76 (68 – 78)	70 (69 – 79)
Gender		
Male	9	3
Ethnicity		
Oceanian (Australia or New Zealand)	11	6
North-West European	2	3
Marital status		
Married or de facto	9	9
Separated or divorced	2	–
Widowed	2	–
Relationship with the patient		
Wife/husband	–	8
Son/daughter	–	1
Living with the patient?		
Yes	–	8
No	–	1
Time spent together weekly		
>40 hours	–	7
20–40 hours	–	1
10–20 hours	–	1
mMRC Score at baseline		
3	13	–
AKPS		
50	3	–
60	6	–
70	3	–
80	1	–

AKPS, Australian Karnofsky Performance Status; mMRC, modified Medical Research Council.

(table 3). The concept of *net effect* emerged from the integration of these four themes, describing the interplay of different factors that contribute to patients' decisions whether or not to continue regular, low-dose, sustained-release morphine.

### Theme 1: Receptivity and knowledge

Before enrolling in the trial, most participants were aware that morphine was a potent painkiller but they had never heard about its potential role in breathlessness. As a result, most patients and caregivers reported they did not know what to expect but they were hopeful it could help reduce breathlessness.

I really didn't know what to expect. (...) But I was hoping it could help me breathe better... (Patient 4)  
Yes, I'd heard about morphine, but not for that reason (breathlessness)... I knew about it for pain. But I was hoping it could help with the shortness of breath. (Carer 11)

Few patients were concerned with addiction or associated morphine with end of life before participating in the trial. These patients raised these concerns with their clinicians/study staff who demystified morphine-related fears, namely by highlighting the small, regular doses used in the context of breathlessness.

It got a perception that morphine was one of those interesting drugs that had both benefits and downsides (...) But also morphine was one that in some cases (was a prelude to) death. I heard about it for people who were terminal. (Patient 2)

No really, my only concern was 'hang on a minute, is this an addictive drug?' And P. and U. (study staff) said 'addiction is not going to be a problem with these doses. It will either help you or it won't. And I trusted them. (Patient 6)

Compared with patients, caregivers had less concerns about morphine prior to trial commencement. Most expressed complete trust in the study procedures and were happy for having the opportunity to try a medication that could potentially help to reduce the symptom of chronic breathlessness.

No, I was not concerned (about addiction). I didn't even think about that! (laughing) I mean, I knew it was an addictive drug, but not in very small doses apparently. I think I've got quite a lot of confidence in these studies because I know they have to go through quite a rigorous approval process. They wouldn't be able to put anyone on it if there was any real danger. (Caregiver 13)

### Theme 2: Function as a priority

Some patients described symptomatic benefit with the study medication, including not only an improvement in breathlessness but also in other symptoms (eg, pain and cough), as well as better sleep. Some patients found it difficult to pinpoint specific improvements, but explained they improved overall. All patients who described symptomatic improvement were taking sustained-release morphine 8–24 mg.

Well, when you wake up gasping... It's not a great way of waking up, I can tell you! It happens occasionally now, but not much anymore. While before it was quite frequent, once or twice every week. I get one of those, every couple of months now. I don't know how morphine does this but I am not arguing because it works (laughing)! (Patient 3 – maximum morphine dose 8 mg)



**Table 2** Individual patients' benefits, harms and outcomes reported by dose in the double-blind, placebo-controlled randomised trial of regular, low-dose sustained-release morphine for the symptomatic reduction of chronic breathlessness in people with chronic obstructive pulmonary disease (COPD)

Participant	Dose of morphine on trial				Extension	Benefits reported	Harms reported	Outcomes
	Week 1	Week 2	Week 3	Week 3				
Patient 1	Placebo	8 mg	16 mg	16 mg	16 mg (for 6 months)	<ul style="list-style-type: none"> <li>Mild improvement in overall well-being</li> <li>Stable disease with less breathlessness exacerbations and less hospital admissions</li> </ul>	<ul style="list-style-type: none"> <li>Mild constipation resolved with laxatives</li> </ul>	Completed the study; currently taking prescribed morphine
Patient 2	16 mg	16 mg	16 mg	16 mg	16 mg (for 6 months)	<ul style="list-style-type: none"> <li>Reduced breathlessness</li> <li>Reduced cough</li> <li>Dramatic improvement in function</li> <li>Improvement in relationships</li> </ul>	<ul style="list-style-type: none"> <li>Severe constipation resolved with prune juice (no improvement with laxatives)</li> </ul>	Completed the study; currently taking prescribed morphine
Patient 3	Placebo	Placebo	8 mg	8 mg	8 mg (for 6 months)	<ul style="list-style-type: none"> <li>Reduced episodic breathlessness during the night</li> <li>Mild improvement in function</li> </ul>	<ul style="list-style-type: none"> <li>No harms reported</li> </ul>	Completed the study; currently taking prescribed morphine
Patient 4	Placebo	Placebo	Placebo	-	-	<ul style="list-style-type: none"> <li>No benefits reported</li> </ul>	<ul style="list-style-type: none"> <li>No harms reported</li> </ul>	Stopped the study drug after 3 weeks on trial due to lack of benefit
Patient 5	16 mg	16 mg	24 mg	24 mg	24 mg (for 1 month)	<ul style="list-style-type: none"> <li>Mild improvement in breathlessness</li> </ul>	<ul style="list-style-type: none"> <li>Constipations that did not resolve with laxatives</li> </ul>	Stopped the study drug after 1 month on the extension phase due to lack of benefit and persistent constipation
Patient 6	8 mg	16 mg	24 mg	24 mg	24 mg (for 6 months)	<ul style="list-style-type: none"> <li>Reduced breathlessness</li> <li>Clear improvement in function</li> <li>Appetite loss (led to weight loss)</li> </ul>	<ul style="list-style-type: none"> <li>Moderate constipation, which became mild with laxatives</li> </ul>	Completed the study; currently taking prescribed morphine
Patient 7	16 mg	24 mg	32 mg	-	-	<ul style="list-style-type: none"> <li>No benefits reported</li> </ul>	<ul style="list-style-type: none"> <li>Constipation that did not resolve with laxatives</li> </ul>	Stopped the study drug after 3 weeks on trial due to lack of benefit and persistent constipation
Patient 8	8 mg	8 mg	8 mg	8 mg	8 mg (for 6 months)	<ul style="list-style-type: none"> <li>No benefits reported</li> </ul>	<ul style="list-style-type: none"> <li>Constipation that never resolved with laxatives</li> </ul>	Completed the study; decided not to continue morphine due to lack of benefit and constipation that never fully resolved
Patient 9	Placebo	8 mg	8 mg	8 mg	8 mg (for 3 months)	<ul style="list-style-type: none"> <li>No benefits reported</li> </ul>	<ul style="list-style-type: none"> <li>No harms reported</li> </ul>	Stopped the study drug after 3 months on the extension phase due to lack of benefits
Patient 10	8 mg	8 mg	8 mg	8 mg	8 mg	<ul style="list-style-type: none"> <li>No benefits reported</li> </ul>	<ul style="list-style-type: none"> <li>No harms reported</li> </ul>	Completed the study; decided not to continue morphine due to lack of benefits
Patient 11	Placebo	Placebo	Placebo	Placebo	Placebo (for 1 month)	<ul style="list-style-type: none"> <li>No benefits reported</li> </ul>	<ul style="list-style-type: none"> <li>Constipation that did not resolve with laxatives</li> </ul>	Stopped the study drug after 1 month on the extension phase due to lack of benefit and persistent constipation
Patient 12	8 mg	16 mg	24 mg	24 mg	24 mg (for 6 months)	<ul style="list-style-type: none"> <li>Improvement in chest pain</li> </ul>	<ul style="list-style-type: none"> <li>No harms reported</li> </ul>	Completed the study; currently taking prescribed morphine
Patient 13	Placebo	8 mg	16 mg	16 mg	16 mg (for 6 months)	<ul style="list-style-type: none"> <li>No benefits reported</li> </ul>	<ul style="list-style-type: none"> <li>No harms reported</li> </ul>	Completed the study; currently taking prescribed morphine.

**Table 3** Comparative analysis of findings from patients and caregivers in a qualitative substudy embedded in a large randomised, placebo-controlled trial of regular, low-dose, sustained-release morphine for the symptomatic reduction of chronic breathlessness in people with chronic obstructive pulmonary disease (COPD)

Patients' and caregivers' themes	Patients' subthemes	Caregivers' subthemes
1. Receptivity and knowledge Both patient and caregiver are receptive to sustained-release morphine for breathlessness	<ul style="list-style-type: none"> <li>▶ Morphine is a potent painkiller</li> <li>▶ Lack of knowledge of morphine for breathlessness</li> <li>▶ No expectations</li> <li>▶ Fear of addiction</li> <li>▶ Association with end of life</li> <li>▶ Discussion with clinicians helps resolve concerns</li> </ul>	<ul style="list-style-type: none"> <li>▶ Morphine is a potent painkiller</li> <li>▶ Lack of knowledge of morphine for breathlessness</li> <li>▶ No expectation</li> <li>▶ Trust in the study processes</li> <li>▶ Happy to be included in a study that could ameliorate the patient's breathlessness</li> </ul>
2. Function as a priority Functional gains widen the life space of both patients and caregivers	<ul style="list-style-type: none"> <li>▶ Improvements in breathlessness are important</li> <li>▶ Functional gains are important, even if small</li> <li>▶ By improving function, morphine widens patients' living space</li> </ul>	<ul style="list-style-type: none"> <li>▶ Attribute importance to observable benefits with impact on their own lives</li> <li>▶ By improving patients' function, morphine widens caregivers' living space and the number of activities they share</li> </ul>
3. Harmful and helpful side effects Side effects of sustained-release morphine can be harmful or helpful	<ul style="list-style-type: none"> <li>▶ Constipation is common and the only harmful side effect reported</li> <li>▶ Anorexia and decreased pain can be helpful side effects</li> </ul>	<ul style="list-style-type: none"> <li>▶ Distressed with patients' constipation</li> <li>▶ Help patients overcome harmful side effects</li> </ul>
4. Therapy-centred aspects From a practical point of view, sustained-release morphine is easy to adapt to	<ul style="list-style-type: none"> <li>▶ Oral sustained-release morphine is easy to take</li> <li>▶ Distressed with not being able to access morphine after the study</li> </ul>	<ul style="list-style-type: none"> <li>▶ Therapy with oral sustained-release morphine requires no changes in their daily routine</li> <li>▶ Distressed by the return of patients' symptoms after ceasing the trial</li> </ul>

Oh, (I felt) generally better in myself you know? My breathing was perhaps a little better, but I felt more alive I suppose you could say... Yeah, just felt better in myself. (Patient 8 – maximum morphine dose 8mg)

In most cases, caregivers' perceptions of improvement/non-improvement matched patients' descriptions. However, caregivers attributed more importance to practical outcomes that had more impact on their own lives. For example, one caregiver reported that despite no symptomatic improvement in breathlessness with the study medication, the patient had stopped having breathlessness exacerbations resulting in hospital admissions. For this caregiver, this was the main advantage of taking morphine, which was not reported by the patient.

We were on the morphine, I believe. That's only a suggestion, but she sort of didn't go backwards all the time for the 6 months (...) Everyone commented (...) she has better colour. I am confident she will hold her own now. (Caregiver 1 – maximum morphine dose 16mg)

Some participants reported that taking the study medication resulted in patients' function improving, which expanded both patients' and caregivers' 'living space' (ie, the actual physical space in which they move and have social interactions) because of easier access to the world.<sup>4</sup> Different patients reported different degrees of functional improvement. However, even small functional

gains were important for both patients and caregivers. Patients experiencing functional benefit were mostly taking sustained-release morphine 16–24mg.

Climbing a set of stairs was difficult. There were steps up from the Festival Theatre to King William road, three flights... I would try going up those but it took at least three steps 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. (Patient 2 – maximum morphine dose 16mg)

He can walk to the letter box to get the letters (...), so he is doing that which he didn't do before. Yeah, so there was a marked improvement. (Caregiver 6 – maximum morphine dose 24mg)

Patients' functional gains had a positive impact on caregivers' lives, who also saw their living space widen as well as the range of daily activities they were able to share with the patient.

Going for a walk for instance was really hard work for him so I worried the whole time. So it was not really very enjoyable. Now, we go out more, we enjoy life more, because we are not constantly worried. That's just been amazing! (Caregiver 2 – maximum morphine dose 16mg)

Participants describing no changes in breathlessness or function were almost all taking placebo or very small doses of sustained-release morphine (8mg).

He's just gone on the same. (Caregiver 8 – maximum morphine dose 8mg)

### Theme 3: Harmful and helpful side effects

Despite being given blinded laxatives as part of the trial, constipation was the only harm reported by participants. For some patients, additional doses of open-label laxatives helped, while others reported relief with prune juice. Some patients withdrew from the trial due to unmanageable constipation, without any significant improvement in breathlessness. Patients with unresolved constipation were more likely taking higher doses of sustained-release morphine (24–32mg).

Constipation was the downside. That was big downside! Before it all started, I could go to the toilet in the morning right after breakfast. And later in the afternoon or early evening, I had to go again. But once, I started, it took me 2 to 3 days to get before I could get rid of it. And that continued all the way through. I felt very bloated. (Patient 5 – maximum morphine dose 24mg)

Constipation was also distressing for caregivers who tried to step up and help the patients to the best of their abilities. In some cases, they were unable to improve patients' symptoms despite their best efforts. In other cases, caregivers were essential in the management of harms.

It (constipation) was bothering him a lot... I tried to give him more roughage but his appetite is very poor so what can you do? If he says 'I don't want to take it' you can't you know? (...) I worries me sometimes. (Caregiver 8 – maximum morphine dose 8mg)

He spoke with U. (study nurse) and she told him to take prune juice, which he has done to good effect. And that's probably the only thing that's really helped. All the medication that he had to take with the trial didn't really do much at all. So I've been cooking prunes madly and he's been having those. And that helped a little bit and he's on the prune juice now and I believe that's working much better. (Caregiver 2 - maximum morphine dose 16mg)

Some side effects were reported as positive and an incentive to continue the study medication. One patient and his caregiver reported mild-to-moderate anorexia with the study medication, which prevented him from snacking between meals (morphine 24mg). As a result, he experienced significant weight loss allowing him to move more freely. Another patient and her caregiver reported improvement in other symptoms (eg, thoracic pain, cough), which motivated her to continue taking the medication (morphine 24mg).

So, one of the side effects that I have with the morphine is it reduces my appetite. It changes your diet. You don't pick, you don't have a piece of cake in the middle of the day and things like that so, I lost 10Kg in weight. And because you lose the weight, it's easier to do your shoes up so physically you just become more active. (Patient 6 – maximum morphine dose 24mg)

She stopped having chest pain since she was put on the medication. She used to get quite bad chest pain at times. That is better, which is good. (Caregiver 12 – maximum morphine dose 24mg)

### Theme 4: Therapy-centred aspects

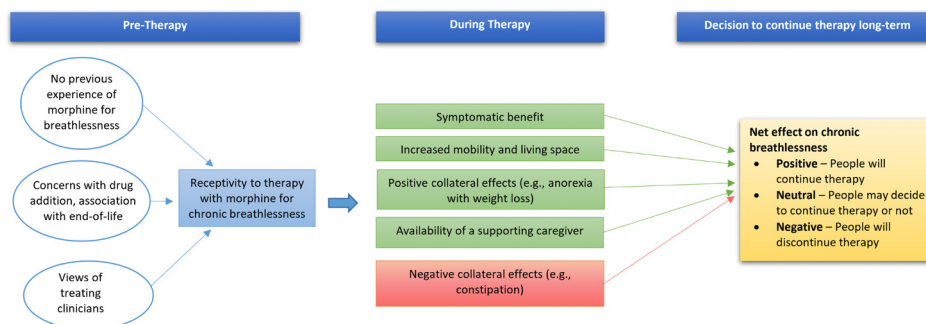
Both patients and caregivers reported that the study medication was easy to take, and did not require any major changes in daily routine. This contributed to maintaining people's long-term adherence to the study medication, even after study cessation.

That was quite easy (taking the study medication) because he just used to take it with all his other medications. So that was no problem. (Caregiver 5 – maximum morphine dose 24mg)

Even though I didn't find it (morphine) helpful, I might have been on placebo. And it's easy enough to give it a try, you know? (...) Now, I am taking (sustained-release) morphine 10mg a day. I will try it for 2 months and then I will have a discussion with S. (respiratory physician) and if she thinks I should continue on it, then I will. (Patient 13 – maximum morphine dose 16mg)

For some people who had benefit, getting a morphine prescription after the trial was difficult, partially because sustained-release morphine was not approved by any regulatory body at that time. Patients describe some clinicians were reluctant to provide a prescription, due to lack of a registered indication for breathlessness and fear of potential harms. Thus, morphine prescribing resulted from discussions and negotiation between patients, caregivers, the research teams and general practitioners.

Well, I think mine (general practitioner) is courageous, he's been prescribing it (morphine) based on a phone call with (the study investigator). (...) Besides I can be very persuasive if I put my mind to it. I just said to him: 'It is very simple, do you want me suffocating quietly here and there on a regular basis, or do we use something that we now know it works?' I can understand it (the reluctance), but, I am not prepared to suffer like I am suffocating here because you have got some moral idea that you don't think it's good for me. You think it's better for me to suffer than have the morphine, I am sorry but I am in her and I am gonna disagree with that argument. (Patient 3 – maximum morphine dose 8mg)



**Figure 2** Factors conditioning the net effect of regular, low-dose, sustained-release morphine for breathlessness.

Difficulties in accessing a prescription for sustained-release morphine also had implications for caregivers, whose distress increased as patients revert to their previous state before initiating sustained-release morphine.

Now he is sleeping like a baby again... But when he stopped (the study), he could not sleep and I could not sleep... It was awful. (Caregiver 6 - maximum morphine dose 24mg)

### Emerging concept: net effect

In addition to the findings presented above, the concept of ‘net effect’ (ie, the perceived effect experienced with the study medication after weighing benefits and harms) emerged from examining the relationship between themes, subthemes and the decision to continue taking sustained-release morphine after study completion (figure 2). People who experienced breathlessness improvement, and especially functional improvement, were more likely to continue the study medication. In contrast, people experiencing constipation were more likely to discontinue the study medication, particularly if refractory to symptomatic treatment, reflecting a narrower therapeutic window for some people.<sup>21</sup> For some people reporting breathlessness improvement, severe constipation prevented them from continuing the study medication. Those who experienced functional improvement were more tolerant of constipation for which they explored different therapeutic options, describing it as ‘a small price to pay’ to get the benefits of morphine. Patients who did not experience any benefits or harms were generally open to try morphine post-trial because they were unsure if they were taking the active medication or placebo (table 2).

Of the four patients living alone, only one was taking prescribed morphine after study completion. Conversely, six out of nine patients living with a caregiver chose to take morphine after the study; of the three who did not, two were on placebo during the trial.

## DISCUSSION

Patients’ choice to continue the study medication seems to be motivated by the experienced net effect (weighing benefits and harms). Benefits included breathlessness

improvement, increased mobility and positive side effects such as improved sleep at night; constipation was the only harm reported. Caregivers’ and patients’ experiences are similar, although caregivers tend to focus more on observable benefits which made a difference in their own lives. Caregivers are critical in helping manage regular, low-dose, sustained-release morphine harms and seem to contribute to the likelihood of continuing this medication in the long term. Participants’ experiences seem to vary according to morphine doses. Generally, people taking placebo or sustained-release morphine 8mg were less likely to report benefits or harms. People taking 16mg and 24mg were more likely to experience benefits, but also side effects (beneficial or harmful). The only participant taking sustained-release morphine 32mg experienced only harms.

The concept of net effect when beneficial has been used to explain people’s choices of sustained-release morphine versus placebo for chronic breathlessness.<sup>21 24</sup> This study saw *net effect*, with positive, negative or neutral outcomes which, in turn, drive decisions to continue or cease the study medication. From the participants’ perspective, although symptomatic improvement was essential, better function was the main driver of perceived benefit. This aligns with previous work describing the importance of independence and mobility for patients with COPD who become increasingly more restricted as the disease progresses.<sup>3 35</sup> Up until now, intensity of breathlessness measured with unidimensional breathlessness scales has been used as the preferred outcome of measure in RCTs of opioids for chronic breathlessness. Findings from this study suggest that primary outcome measures focused on function may be more relevant for this population. This hypothesis is further supported by a previous RCT of people with COPD and chronic breathlessness in which regular, low-dose, sustained-release oral morphine has been shown to significantly improve health status using the COPD assessment test, especially when assessing walking upstairs or hills.<sup>36</sup> As a result, it is important to select primary outcome measures evaluating function in future studies evaluating opioids for chronic breathlessness.

For caregivers, observable gains in function are also critical not only because they see their loved ones become more independent, but also because their own



living space increases.<sup>4</sup> In some cases, caregivers provide unique perspectives on the benefits and downsides of therapy, that the patient alone is unable to provide. Since chronic breathlessness infiltrates the lives of both patients and caregivers, it is important to include caregivers' perspectives in the assessment or reassessment of any new therapy, in order to get a full picture of its effects.<sup>37</sup>

This study brings a new lens on side effects caused by regular, low-dose, sustained-release morphine. First, while some side effects were experienced as harmful, others were perceived as helpful. Importantly, clinicians' and patients' perceptions are not always aligned, particularly in symptom evaluation.<sup>38,39</sup> This study highlights that side effects typically perceived as harmful by clinicians may contribute to treatment success in some cases. Second, sedation and nausea were not reported in this study. These are frequent opioid side effects particularly during therapy initiation and upward titration. The use of very small doses of sustained-release morphine (8mg) and controlled upward titration (maximum 16mg weekly) may have contributed to these findings. However, constipation was common in this study and one of the few side effects contributing to discontinuing therapy. In line with previous findings, managing constipation might be critical to influence adherence to therapy in people taking regular, low-dose, sustained-release oral morphine for chronic breathlessness.<sup>21</sup> Sustained-release morphine 8mg caused few side effects but was also unlikely to improve breathlessness. With such small doses, the amount of morphine binding to  $\mu$ -opioid receptors may be insufficient to trigger any clinical effect.<sup>40</sup> Slow upward titration allows the development of tolerance to morphine, which can reduce side effects experienced after abrupt introduction of higher doses.<sup>40</sup>

This qualitative study shows that most people are unaware of the use of sustained-release morphine for chronic breathlessness. This may represent a practical advantage in the clinical setting given that patients may be intrigued about its potential effects and less focused on opioid-related concerns (eg, addiction).<sup>41</sup> Additionally, for people who do express concerns, information about the low doses used for chronic breathlessness may be sufficient to reassure them. In any case, support from treating clinicians seems to be critical *before* initiating the study medication.<sup>42,43</sup> However, *after* experiencing net benefit, some participants may want to continue taking morphine even when they face clinicians' resistance. This requires clinicians to be well informed and prepared to deal with such challenges. Overall, caregivers were less concerned about side effects and more willing to try a new medication that could improve breathlessness. This is not surprising as caregivers are often severely distressed by patients' breathlessness and their functional decline.<sup>44</sup> It is likely they are receptive to any treatment aiming to reduce patients' suffering.

Overwhelmingly, participants reported that regular, low-dose, sustained-release morphine was easy to take

and therefore not an obstacle to therapy continuation. Sustained-release formulations are often well tolerated because they require less frequent administrations and do not require interruptions to sleep when compared with immediate-release morphine (taken approximately every 4 hours).<sup>45</sup> For people who experienced benefit, getting a prescription of sustained-release morphine after the study was difficult and frustrating. This was partially attributed to a lack of a formal indication and registration for chronic breathlessness at that time. However, clinicians are often resistant to prescribe morphine in people with COPD due to fear of respiratory depression and overall concerns related with opioid safety.<sup>46,47</sup> Such fears may still persist after sustained-release morphine approval, and may require interventions aiming to inform and support clinicians. Moreover, despite supportive international guidelines,<sup>15,16</sup> regular, low-dose, sustained-release morphine is still not registered for chronic breathlessness outside Australia. Thus, accessing this treatment it is still a challenge for many patients with disabling breathlessness and their clinicians.

This study also highlighted the role of caregivers, who are often the only source of support for these patients, having a crucial role in helping to manage the side effects of sustained-release morphine therapy. This is in line with previous work describing the role of carers in the process of adaptation to breathlessness, requiring extreme flexibility and rapid adjustment to the unpredictable challenges imposed by breathlessness.<sup>48</sup> Given the caregiver's role in facilitating coping with constipation and the proportion of patients with a caregiver willing to continue morphine after the trial, this work also suggests that the caregiver may be a key player in patients' adherence to treatment with regular, low-dose, sustained-release morphine. The relevance of caregivers in facilitating patients' adherence to therapy was highlighted before,<sup>22</sup> suggesting that the caregiver may not only be a care recipient but also a potential co-worker with clinicians.<sup>49</sup>

This was the first study focusing on people's experiences with the current recommended formulation and doses of sustained-release morphine for chronic breathlessness.<sup>20</sup> People had recently started the medication, and some had chosen to discontinue it. This provided a range of experiences (positive and negative) which were not captured before.<sup>23</sup> Participants and researchers were blinded, which reduced bias while selecting and interviewing participants. One limitation of this study is that interviews were conducted by a non-native English speaker (DF). Any misunderstandings between interviewer and interviewees were mitigated by interview and transcription checking performed by a native English-speaker researcher (AH). The qualitative design limits generalisability of the findings. However, data checking/analysis involved researchers with different backgrounds, reducing the risk of bias. All participants had agreed to be part of the trial, which could have led to selection bias of people who were willing to accept morphine. All



participants completed at least 3 weeks on the BEAMS Trial. Perceptions from this group may not reflect the views of all people with COPD and chronic breathlessness.

This study has important implications for future research and clinical practice. The concept of 'net effect' highlights key factors influencing the decision to continue therapy with regular, low-dose, sustained-release morphine and may be useful to understand people's choice to continue other therapies for chronic breathlessness. Considering that caregivers are instrumental in alleviating harms associated with regular, low-dose, sustained-release oral morphine, it is essential to investigate caregivers' needs in this context and understand how patient and caregiver can better cooperate in the management of this medication. It is also imperative to understand how to facilitate coping with therapy for patients who do not have a caregiver. In clinical practice, discussing the potential role of regular, low-dose, sustained-release oral morphine to reduce chronic breathlessness and highlighting the small doses required for this indication may increase patients' and carers' acceptance of this medication in clinical practice. For patients taking regular, low-dose, sustained-release oral morphine, carers are active agents in ameliorating the impact of harms associated with therapy. Informing and preparing carers for potential harms of regular, low-dose, sustained-release oral morphine may reduce their anxiety and empower them to better respond to such situations.

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