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Early View

Research letter

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The effect of regular, low-dose, sustained-release morphine on routine physical activity in people with persistent breathlessness– a hypothesis-generating study

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To the editor:

Chronic breathlessness, which may be better described as *persistent breathlessness* to optimise applicability to different languages, is a frequent cause of disability in chronic obstructive pulmonary disease (COPD)[1]. In many people with advanced COPD, optimising treatment for the underlying causes of breathlessness and employing non-pharmacological approaches doesn't achieve symptom control[2]. Some people with persistent breathlessness may benefit from regular, low-dose, sustained-release (SR) morphine[3]. Importantly, changes in unidimensional breathlessness measures do not always reflect the patient's perspective of benefit[4]. Optimal ways of measuring meaningful changes in persistent breathlessness are debated[5], but small funtional gains are valued by patients[6]. These gains may be reflected in periods of more intense energy expenditure, allowing people to better maintain independence.

The aim of this hypothesis-generating sub-study was to explore the effect of regular, low-dose, SR morphine on actigraphy-measured physical activity.

This was a sub-study of a placebo-controlled randomised controlled trial (RCT) of regular, low-dose, SR morphine for persistent breathlessness (Breathlessness Exertion and Morphine Sulphate [BEAMS] study)[7]. Participants had COPD and a modified Medical Research Council (mMRC) scale (measuring level of exertion limited by breathlessness) $\geqslant$3 despite optimal treatment of underlying causes[7]. Participants were randomised at baseline to: placebo, 8mg or 16mg of once-daily SR morphine for one week. In weeks 2 and 3, there were two additional randomisations, each of which added placebo or SR morphine 8mg to the previous dose. For the third week, morphine doses were placebo, 8mg, 16mg, 24mg or 32mg (1:12 chance of being on placebo). Participants were asked to wear an actigraphy device (FitBit^{R}) in the last day of baseline period, weeks 1 and 3.

Daily steps were a co-primary outcome of the study[7,8]. This analysis explores additional FitBit^{R} actigraphy measures based on each person's resting metabolic rate (MET) for at least 10 continuous minutes[9]: total and active caloric expenditure; and number of active minutes (lightly active = 1.5-<3METs; fairly active 3-6 METs; very active ≥6 METs).

Differences in activity measures by study arm are described and any relationship with global impression of change(GIC; 7-point Likert scale) explored[10].

Of 156 trial participants, 75 did not provide actigraphy data (reasons: battery failure; equipment failure; failure to download data due to incorrect log-in, firewall protection, and FitBit^{R} updates with loss of data). Eighty-one participants provided complete actigraphy data for analysis: mean±SD age was 73.9±7.3 years; 59.3% were male; 19.8% had mMRC 4 breathlessness scores and 38.8% used supplementary oxygen; mean Australian-modified Karnofsky Performance Status was 63.5±8.1 and mean baseline *worst breathlessness* in the previous 24 hours was 6.2±1.6 points on the 0-10 numerical rating scale (NRS). Four participants withdrew in Week 1 due to harms; 77 provided Week 1 actigraphy data (placebo n=27; morphine 8mg n=30; morphine 16mg n=30); and 35 on Week 3 (placebo n=4; morphine 8mg n=8; morphine 16mg n=10; morphine 24mg n=10; morphine 32mg n=3).

Differences between Baseline and Week 1 were (mean±SD): total calories -53.2±426.5, activity calories +197.5±651.8, minutes lightly active +54.9±113.8, minutes fairly active +1.2±54.9, minutes very active +4.0±22.4. There was no relationship between study arm and any of the actigraphy measures.

Differences between Baseline and Week 3 were (mean±SD): total calories -63.1±368.2, active calories +152.2±621.0, minutes lightly active +36.4±118.3, minutes fairly active -1.2±26.6, minutes very active +2.9±14.1. For active calories, all morphine arms tended to improve from baseline to Week 3, while placebo was unchanged. For minutes lightly active, there was a larger improvement in the morphine arms than the placebo arm. For all activity measures, placebo and active arms need to be studied in a larger cohort, for longer than three weeks of therapy as no ceiling signal is seen (Figure 1 [top]).

Improvements in active calories and minutes lightly active seemed to relate toperception of benefit only at Week 3 (Figure 1 [bottom]).

These hypothesis-generating analyses indicate that SR morphine may have a role in improving functional capacity in those able to continue taking this medication for at least

three weeks, reflected in the number of active calories and minutes lightly active. These outcomes are likely to be meaningful for people with severe COPD-associated persistent breathlessness[6].

Evidence from effectiveness RCTs for regular, low-dose, SR morphine for persistent breathlessness is conflicting. Currow *et al* reported that SR morphine did not improve *breathlessness now* compared with placebo after seven days of treatment[8,11]. Verberkt *et al* reported that SR morphine improved health status measured with the COPD assessment test (CAT) at 4 weeks[3]. Three questions ensue: 1) What are the most meaningful outcomes for people with persistent breathlessness?, 2) When should those outcomes be measured? and 3) How do we identify people most likely to experience net benefit?

It is possible that SR morphine may benefit people with persistent breathlessness by increasing the threshold before breathlessness becomes intolerable, allowing people more intense physical activity[12]. As people exert themselves to new levels of physical activity, the same intensity of breathlessness may limit them, leading to no change in breathlessness[12], which could explain the negative results in effectiveness RCTs[8, 11].

Given these results, breathlessness assessments should be standardised to levels of physical activity[12]. Understanding how best to incorporate momentary breathlessness scores into the evaluation of the symptom requires additional work given the influence of daily mean, peak and end values experienced leading up to assessments [13].

Verberkt *et al* results may be positive because the CAT includes activity-related questions[3]. Number of daily steps in BEAMS did not show any signal of effect[8] but people who report larger benefit with SR morphine often describe small but meaningful gains in daily activities, such as being able to walk to the letterbox or climb stairs[6]. Thus, it is likely that “large improvements” from the patients’ perspective translate into being able to engage in short periods of increased physical activity to perform tasks important to them. These may include self-care activities while seated requiring very few steps. Possibly, such differences are more accurately reflected in the number of *active calories* and *active minutes*, rather than by *daily steps*.

Of note, the study by Verberkt *et al* showed a significant improvement in *worst breathlessness* in the sub-group of participants with mMRC 3-4, after four weeks. Together with findings from this sub-study, these results may indicate that the full extent of *functional improvement* produced by SR morphine may only be seen after a few weeks of regular therapy[3]. An open-label study of regular low-dose, SR morphine for persistent breathlessness reported that responses to SR morphine, reflected in reductions in unidimensional breathlessness measures, occurred within the first 24-48 hours[14]. However, changes in function may take longer to develop and be incremental as people take time to improve physical conditioning Exploring different primary outcomes measures for persistent breathlessness, particularly those related with short bouts of more intense physical activity, deserves further exploration in future qualitative and quantitative studies[15].

In summary, this study is limited by the relatively small number of participants per arm and results are not generalisable. However, it is possible that measuring routine physical activity may be useful in evaluating interventions seeking to reduce persistent breathlessness. This need to be investigated in future studies.

Conflict of Interest

ME and DF declare no conflict of interests. MJ was a paid clinical consultant to Mayne Pharma. DJ received research grants from the Netherlands Organisation for Health Research and Development (ZonMw), Stichting Astmabestrijding and NRS Award; provided paid lectures from Boehringer Ingelheim, Chiesi, Abbott; participated in the BETTER-B Trial Steering Committee, Scientific committee of the Wolfson Palliative Care Research Centre, Hull, UK, ERS Taskforce. DC is on the Advisory Board member and paid consultant for Helsinn Pharmaceuticals; a paid consultant and receive payment for intellectual property with Mayne Pharma International Pty Ltd; a paid subcontractor to Nous Group Pty Ltd; a paid Board member for icare Dust Diseases Care NSW; unpaid Board member/Director for Chris O'Brien Lifehouse; Board member of IHMRI.

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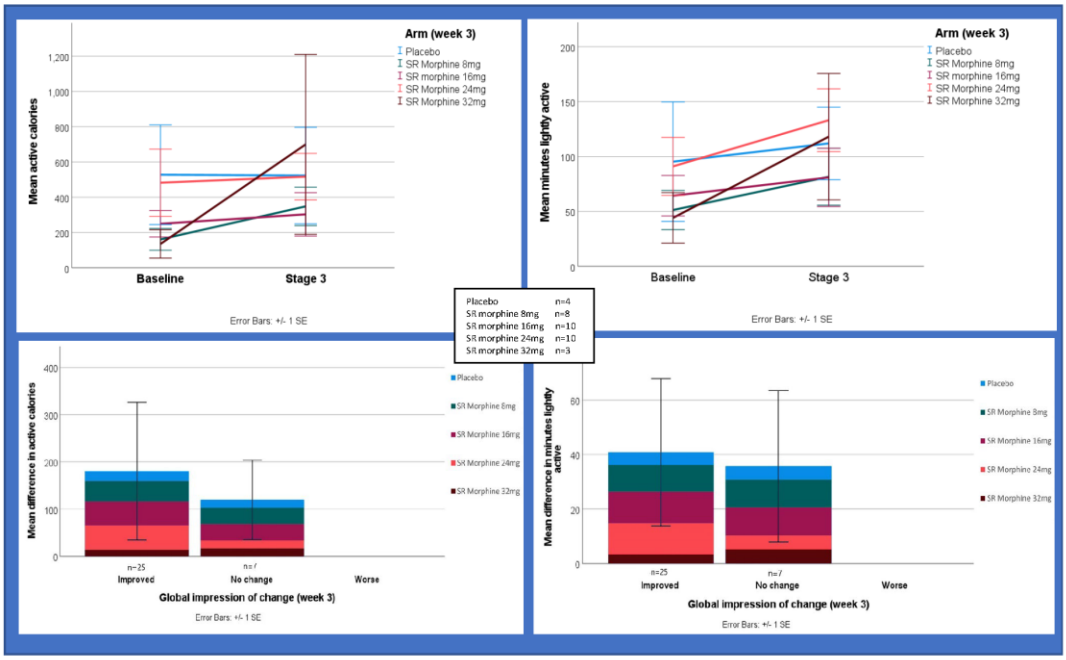

Figure 1 – Arm differences in mean activity calories (*top left*) and mean minutes lightly active (*top right*) from baseline to the end of week 3. Relationship between the mean difference in active calories (*bottom right*) and mean difference in minutes lightly active (*bottom right*) and global impression of change (GIC) at the end of week 3.

Colours represent different arms. GIC categories were collapsed into Improved (minimally to very much improved), No change and Worse (minimally to very much worse). Three participants did not provide global impression of change.