Original Article

To What Extent Do the NRS and CRQ Capture Change in Patients' Experience of Breathlessness in Advanced Disease? Findings From a Mixed-Methods Double-Blind Randomized Feasibility Trial

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Abstract

Context. Chronic or refractory breathlessness is common and distressing. To evaluate new treatments, outcome measures that capture change in patients' experience are needed.

Objectives. To explore the extent to which the numerical rating scale (NRS) worst and average, and the Chronic Respiratory Questionnaire capture change in patients' experience during a trial of mirtazapine for refractory breathlessness.

Methods. Convergent mixed-methods design embedded within a randomized trial comprising 1) semi-structured qualitative interviews (considered to be the gold standard) and 2) outcome measure data collected pre- and post-intervention. Data were integrated, exploring examples where findings agreed and disagreed. Adults with advanced cancer, chronic obstructive pulmonary disease, interstitial lung disease, or chronic heart failure, with a modified Medical Research Council dyspnea scale grade 3 or 4 were recruited from three U.K. sites.

Results. Data were collected for 22 participants. Eleven had a diagnosis of chronic obstructive pulmonary disease, eight interstitial lung disease, two chronic heart failure, and one cancer. Median age was 71 (56–84) years. Sixteen participants were men. Changes in the qualitative data were commonly captured in the NRS (worst and average) and the Chronic Respiratory Questionnaire. The NRS worst captured change most frequently. Improvement in the emotional domain was associated with physical changes, improved confidence, and control.

Conclusion. This study found that the NRS using the question "How bad has your breathlessness felt at its worst over the past 24 hours?" captured change across multiple domains, and therefore may be an appropriate primary outcome measure in trials in this population. Future work should confirm the construct validity of this question. J Pain Symptom Manage 2019;58:369–381.

Key Words

Breathlessness, shortness of breath, advanced disease, outcome measure, randomized controlled trial

Introduction

Breathlessness is common and distressing in advanced disease,[1–3] resulting in anxiety, physical inactivity, and a poorer quality-of-life.[4–6] It is a common reason for emergency hospital admission, and remains a challenge to assess and treat.[7] There are few effective pharmacological treatment options, with some evidence for opioids, but concerns regarding side effects and small effect sizes.[8] New effective treatments are urgently required, and drugs which may modify processing and perception of afferent information in the brain such as antidepressants have been proposed.[9] Breathlessness is a subjective experience, derived

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from interactions between multiple physiological, psychological, social, and environmental factors with evolving terminology (Fig. 1).[10] It is what the patient says it is and cannot be measured fully using physiological variables. Although there are a variety of patient-reported outcome measures validated for breathlessness,[11–13] there remains little consensus about which to use and when.[14] The treatment being evaluated can be an important consideration when selecting which outcome measure to use; some treatments may reduce the intensity of breathlessness, others may reduce the associated distress.

The National Cancer Research Institute Palliative Care Breathlessness Subgroup consensus statement (2009) recommended that breathlessness severity should be assessed in research using a single-item measure, but that researchers should also consider including a measure of fatigue, mastery, emotional state, and sleep.[15] However, people living with advanced disease and breathlessness report concerns across the following six domains of "total breathlessness": 1) physical including function, 2) emotional concerns, 3) social impact, 4) spiritual distress, 5) impact of control in relation to an episode of breathlessness and within the wider context, and 6) context (episodic and/or chronic).[6] Therefore, when testing new treatments it is important to capture change across these domains. The primary outcome measure in breathlessness trials of oxygen, benzodiazepines, and opioids is often a single-item measure, most commonly the numerical rating scale (NRS).[8,16,17]

The NRS is a 0–10 scale with a rating statement or question, anchored by a descriptive statement at each end.[18] The NRS was originally validated against another single-item measure (the visual analog dyspnea scale), and validation was based on correlation between the two measures in patients with chronic obstructive pulmonary disease (COPD) at rest and following exercise.[18–20] The NRS was validated with the following statement: "Indicate how much shortness of breath you are having right now."[18] However, the statement or question which accompanies the 0–10 scale has evolved over time, and intervention studies increasingly report an assessment of average (NRS average) and worst (NRS worst) breathlessness over the past 24 hours.[20–31] Even across studies there are subtle differences in the wording of the accompanying statement or question. Despite no validation of these adapted versions they are increasingly adopted as the primary outcome in breathlessness trials. Appendix I demonstrates the variability of rating statement/questions used across a number of studies. A comparison of studies assessing pain intensity has identified similar discrepancies, with unidimensional scales varying in length, period, number of response options, and verbal descriptors.[32] The review highlights the importance of psychometric testing, and suggests that consistency of wording, time frame, and format is important.[32]

Breathlessness: a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity(22)

Refractory breathlessness: breathlessness which persists despite maximal medical and other therapy being given for the underlying condition(23)

Chronic breathlessness: breathlessness which persists despite optimal treatment of the underlying pathophysiology and results in disability for the patient(24)

Episodic breathlessness: episodes of worsening intensity or unpleasantness beyond usual fluctuations in the patient's perception(25)

Fig. 1. Common definitions.[52–55]

In addition, breathlessness trials sometimes include a multidimensional measure as a secondary outcome, one example of this is the Chronic Respiratory Questionnaire (CRQ). The CRQ is a broader health-related quality-of-life questionnaire, which measures the following four domains: dyspnea, fatigue, emotional function, and mastery.[33] The CRQ has been validated in a series of studies spanning item development, reproducibility, responsiveness, and validation against other questionnaires including a patient global rating score.[33]

To ensure better quality trials in the future, it is vital to understand whether frequently used measures capture change in patients' experience of breathlessness. This is particularly important for the NRS (average and worst) where wording has evolved and changed since the original validation. This study therefore aimed to explore whether and to what extent three commonly used measures (NRS worst, NRS average, and CRQ) capture change in patients' experience during a randomized trial of mirtazapine for refractory breathlessness.

Methods

Design

Convergent mixed-methods design embedded within a randomized trial comprising 1) semi-structured qualitative interviews and 2) quantitative outcome measure data collected pre- and post-intervention. Data were collected as part of a double-blind randomized feasibility trial of mirtazapine for refractory breathlessness (Fig. 2). Participants were randomized to receive 28 days of trial treatment, either oral mirtazapine or placebo. Ethical approval was received from the U.K. Health Research Authority (16/LO/0091). The trial was prospectively registered on ISRCTN 32236160 and the European Clinical Trials Database (EudraCT no: 2015-004064-11), where

main results are available. Recruitment to the trial occurred between August 2016 and December 2017. The qualitative and quantitative data were collected separately, then integrated and compared in an interpretation phase. The main researcher (NL) remained blinded during data collection and analysis. Examples were explored where the findings from both data sets agreed and where they disagreed.

Setting

Participants were recruited from three U.K. centers, in South London, Nottingham, and Hull. Potential participants were identified through inpatient clinical teams, multidisciplinary team meetings, hospital clinic lists, and hospital databases.

Study Participants and Sampling

Those eligible for the feasibility trial were adults with cancer, COPD, interstitial lung disease (ILD), or chronic heart failure, with a modified Medical Research Council grade 3 ("I stop for breath after walking about 100 yards or after a few minutes on the level") or 4 ("I am too breathless to leave the house" or "I am breathless when dressing"), with no current diagnosis of severe depression, and not currently prescribed an antidepressant medication. For full eligibility criteria see Appendix II.

All participants were informed of the possibility of a qualitative interview when they provided written informed consent for the trial. Purposive sampling was used to achieve maximum variation based on primary diagnosis, trial completion/non-completion, and age (<65 years or >65 years). The sample included participants from both arms of the trial. Participants were approached by telephone or in-person. All participants provided written informed consent before interview.

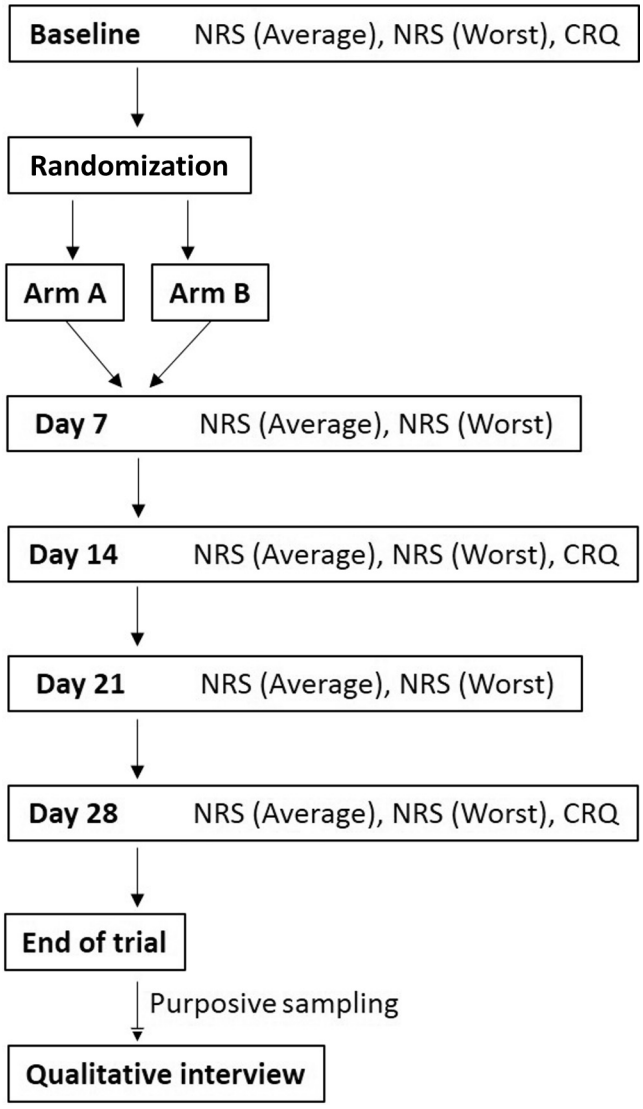

Fig. 2. Trial flow chart. NRS = numerical rating scale; CRQ = Chronic Respiratory Questionnaire.

Data Collection

Quantitative Outcome Measures. The NRS (average and worst) and CRQ were collected as part of the feasibility trial that took place over 35 days, with patient visit contacts at baseline, days 14 and 28, and phone contacts on days 7, 21, and 35 (Fig. 2). In the trial, participants were randomized to receive either mirtazapine or placebo for 28 days, with a final assessment on Day 35.

The NRS was completed at baseline, days 7, 14, 21, and 28. Two NRS rating questions were asked "How has your breathlessness been over the last 24 hours on average?" (NRS average) and "What is the worst your breathlessness has been over the last 24 hours?" (NRS worst). The question was anchored with the statement "not breathless at all" positioned next to number 0, and "the worst possible breathlessness" next to number 10.

The CRQ was completed at baseline, days 14 and 28. The CRQ is a 20-item questionnaire, asking about the last two weeks, with the following four domains: dyspnea (their five most important activities and how short of breath each activity made them feel), fatigue (four questions), emotional function (seven questions), and mastery (four questions). Each question is scored on a 7-point Likert scale, higher scores indicated less breathlessness or better quality of life. Mean scores for each domain enable comparisons between domains.[34]

Qualitative Interviews. Qualitative interviews were conducted at the end of the trial. Interviews were conducted in a place of the participants choosing, usually their own home, but some were conducted in hospital. A topic guide was developed based on the literature and refined after feedback from patient representatives and the Trial Management Group (Appendix III). The interview schedule included questions about whether participants had perceived a change during the trial period, and if so, what had changed. Open questions were used to ensure that participants were not restricted in their answers. Interviews were digitally audio recorded and transcribed verbatim. A distress protocol was developed to minimize the risk of potential harm. All interviews were conducted by one researcher (NL) who has a medical background and had completed training in in-depth interviewing. Interviews took place in 2017.

Analysis

The quantitative and qualitative data were collected and analyzed separately, then integrated and compared in an interpretation phase.

Quantitative Outcome Measures. Measures were compared to derive a change score from baseline to Day 28, a period comparable to that asked about in the qualitative interviews. Change was assessed according to the minimal clinically important difference guidance for each questionnaire.[35,36] The NRS was considered to have changed if there was a >1-point change,[35] and the CRQ threshold was >0.5 unit change for each domain.[36]

Qualitative Interviews. The qualitative interviews were analyzed through thematic analysis[37] using NVIVO, version 10 (QSR International (UK) Ltd., Warrington). The main researcher (NL) remained blinded during analysis to reduce the risk of interpretation bias, and improve confidence in the findings.[38,39] Transcripts were read and re-read, and coded inductively for themes relating to change in experience of breathlessness during the trial. Themes were considered within the domains of "total breathlessness" (Fig. 3).[6] Perceived changes were categorized in terms of the extent of the change. This was based on the language used by participants to describe any change they had perceived, for example, "I didn't really feel any different" was coded as no change, "the benefit that I thought I felt was quite small" was coded as small change, and "it has made a big difference" was coded as large change. To improve trustworthiness, the main researcher (NL) remained blinded during data collection and analysis. Three transcripts were double-coded by another researcher (SE) who produced their own coding frame. Areas of agreement and disagreement in particular relating to the degree of change were discussed until consensus was achieved. A reflexive diary was also used.

Integration. Changes in patients' experience of breathlessness were compared at an individual level; that is, where change was seen in the qualitative data, we looked for evidence of change in the quantitative data and vice versa. As patient report is considered the gold standard for assessing breathlessness, we considered the qualitative interview as gold standard in this study.[40] To understand whether and to what extent quantitative measures captured change in patients' experience of breathlessness, we explored examples where findings agreed and disagreed. If both data sets identified change or neither identified change, this was classified as agreement. If one data set identified change but the other did not, this was classified as disagreement. We also considered how change was captured across the domains of "total breathlessness," and whether there were patterns of change across domains.

Results

Qualitative and quantitative outcome measure data were collected for 22 participants (Appendix IV). Eleven had a diagnosis of COPD, eight ILD, two

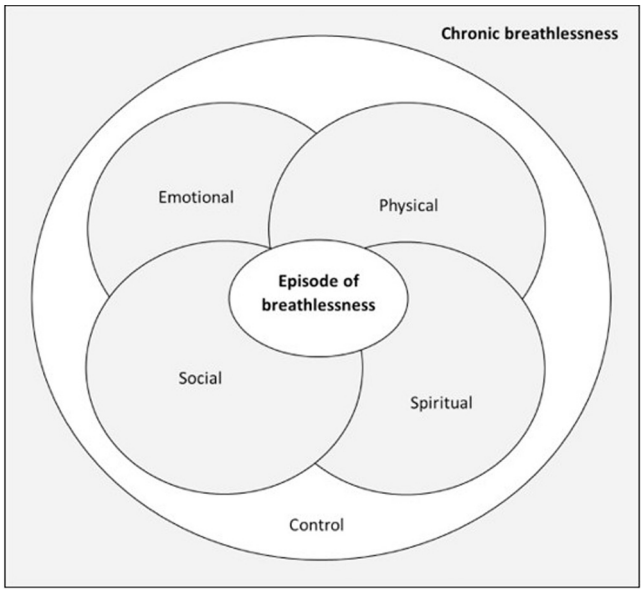

Fig. 3. Model of total breathlessness.[6]

chronic heart failure, and one lung cancer. Median age was 71 years (range 56–84 years). Sixteen were male. Twenty had completed the trial, whereas two withdrew because of reported adverse effects of the trial medication. The mean interview duration was 33 minutes (range 15–104 minutes). Eight of 264 items were missing in the quantitative data. A change score was calculated in the NRS average and worst for 21 of 22 participants and in the CRQ for 19 of 22 participants. The characteristics of participants based on the pre-determined sampling frame are shown in Table 1. The coding frame for the qualitative data is presented in Appendix V.

Patterns of Overall Agreement Between Qualitative and Quantitative Data

Changes in experience of breathlessness for each participant are shown in Table 2. Changes in the qualitative data are categorized in terms of the extent of the change (no change, small change, and large change). Change in the quantitative data is presented as a change score. An assessment of whether the change score is clinically important was calculated using guidance for each individual questionnaire, and also presented. In the qualitative data, 12 participants described changes in their experience of breathlessness during the trial. For the NRS worst and NRS average, there was a clinically important change in 13 and nine cases, respectively. For the CRQ, there was a clinically important change in 16 cases. There was agreement between the qualitative data and the NRS worst in 18 of 21 cases, the NRS average in 16 of 21 cases, and the CRQ in 15 of 21 cases. There was agreement for change or no change in the experience of breathlessness across all measures in 12 cases.

Agreement Between Patients' Experience and Outcome Measures

Participants described change in experience across all domains of "total breathlessness" during the trial (Appendix VI). For some participants, changes were wide-ranging and impacted across several domains. One male participant with COPD described physical changes including better breathing and sleeping, fewer emotional concerns, improved sense of well-being, and greater sense of control. His outcome measure data showed clinically important change in NRS worst, and emotion, mastery, and fatigue domains of the CRQ.

> *Everything was so much better. I would sleep better, so if I sleep better that means by breathing is better when I wake up in the morning, which it never was before. I used to struggle to get up with the breathing … they definitely really helped. Even, even all my friends and neighbours have said how different I am.*
>
> Participant ID 1003

Another participant reported that his breathing was eased by changes across emotional and spiritual domains. His outcome measure data showed a clinically important change in the CRQ emotion, and NRS worst and average.

> *What's the way to describe it, a wave of, wellbeing. Erm. Comfort, happy with my role, erm. It's almost like id got an extra security blanket for, for the period, you know, that's how it felt to me, it was one more thing protecting me. Easing my breathing. That's how it felt to me. It could be wrong, but that's how it felt, I felt it all the way through.*
>
> Participant ID 1009

For others, the change in experience of breathlessness was specific to one domain. It was common for participants to describe improvements within the emotional domain. One male participant with COPD

Table 1
Characteristics of Participants Based on Sampling Frame

	Male	Female
ILD		
<65 yrs old	1	
>65 yrs old	5	3 (1 did not complete trial)
COPD		
<65 yrs old	2	1
>65 yrs old	5	1
CHF		
<65 yrs old		
>65 yrs old	2 (1 did not complete trial)	
Cancer		
<65 yrs old		
>65 yrs old	1	1

ILD = interstitial lung disease; COPD = chronic obstructive pulmonary disease; CHF = chronic heart failure.

Table 2

Change in Qualitative and Quantitative Measures Over Trial Period

ID	Qualitative (Important Domains)	Qualitative (Perceived Change)[a]	Qualitative Direction of Change	NRS (Worst), Range 0–10				NRS (Average), Range 0–10				CRQ (Domains), Range 1–7			
				BL	D28	Change Score	Clinically Important[b]	BL	D28	Change Score	Clinically important[c]	BL	D28	Change Score	Clinically Important[d]
1001	Physical	No change	N/A	7	7	0	No	5	5	0	No	Emotion: 5.4 Mastery: 5.5 Fatigue: 5.0 Dyspnea: 2.4	Emotion: 4.7 Mastery: 3.5 Fatigue: 4.0 Dyspnea: 3.0	−0.7 −2.0 −1.0 +0.6	No No No Yes
1002	Physical Emotional Control	Small change	Easier breathing → increased confidence → increased activity	5	4	−1	Yes	5	4	−1	Yes	Emotion: 4.9 Mastery: 5.5 Fatigue: 4.3 Dyspnea: 3.0	Emotion: 4.1 Mastery: 5.5 Fatigue: 4.5 Dyspnea: 3.4	−0.8 0 +0.2 +0.4	No No No No
1003	Physical Emotional Social Control	Large change	Sleep better → breathing better → less frightened → can do more	8	5	−3	Yes	7	8	+1	No	Emotion: 2.3 Mastery: 2.5 Fatigue: 1.5 Dyspnea: 1.8	Emotion: 4.4 Mastery: 4.3 Fatigue: 4.0 Dyspnea: 2.2	+2.1 +1.8 +2.5 +0.4	Yes Yes Yes No
1004	Physical	Small change	Feeling a little less breathless during daily walk	4	3	−1	Yes	4	2	−2	Yes	Emotion: 5.9 Mastery: 6.0 Fatigue: 4.5 Dyspnea: 3.0	Emotion: 6.7 Mastery: 6.5 Fatigue: 5.8 Dyspnea: 3.2	+0.8 +0.5 +1.3 +0.2	Yes Yes Yes No
1005	Physical	No change	N/A	8	5	−3	Yes	4	3	−1	Yes	Emotion: 5.9 Mastery: 5.5 Fatigue: 2.8 Dyspnea: 4.2	Emotion: 5.3 Mastery: 5.5 Fatigue: 3.3 Dyspnea: 5.6	−0.6 0 +0.5 +1.4	No No Yes Yes
1006	Physical	Large change	Feeling less breathless →not using oxygen → able to walk further	10	7	−3	Yes	9	6	−3	Yes	Emotion: 3.9 Mastery: 3.5 Fatigue: 3.3 Dyspnea: 3.6	Emotion: 4.6 Mastery: 3.5 Fatigue: 3.3 Dyspnea: 2.4	+0.7 0 0 −1.2	Yes No No No
1007	Physical Emotional Social Spiritual	No change	N/A	8	9	+1	No	6	6	0	No	Emotion: 6.4 Mastery: 7.0 Fatigue: 4.0 Dyspnea: 2.2	Emotion: 5.1 Mastery: 6.0 Fatigue: 3.3 Dyspnea: 1.8	−1.3 −1.0 −0.7 −0.4	No No No No
1008	Physical Emotional Social Spiritual	No change	N/A	8	7	−1	Yes	5	6	+1	No	Emotion: 3.4 Mastery: 3.0 Fatigue: 2.8 Dyspnea: 1.4	Emotion: 3.3 Mastery: 2.8 Fatigue: 2.0 Dyspnea: 1.8	−0.1 −0.2 −0.8 +0.4	No No No No
1009	Physical Emotional Spiritual	Small change	Easier breathing → Sense of wellbeing → Can do more	8	5	−3	Yes	6	3	−3	Yes	Emotion: 5.4 Mastery: 5.3 Fatigue: 3.5 Dyspnea: 2.2	Emotion: 6.1 Mastery: 6.5 Fatigue: 5.3 Dyspnea: 4.0	+0.7 +1.2 +1.8 +1.8	Yes Yes Yes Yes
1010	Physical Control	Small change	Less breathless → able to forget breathlessness → feeling of wellbeing	4	2	−2	Yes	2	2	0	No	Emotion: 6.7 Mastery: 5.3 Fatigue: 5.8 Dyspnea: 4.4	Emotion: 6.3 Mastery: 6.0 Fatigue: 5.0 Dyspnea: [e]	−0.4 +0.7 −0.8 [e]	No Yes No [e]

1011	Physical Emotional	No change	N/A	8	8	0	No	4	4	0	No	Emotion: 5.1 Mastery: 3.3 Fatigue: 4.5 Dyspnea: 2.2	Emotion: 6.3 Mastery: 5.3 Fatigue: 5.3 Dyspnea: 4.0	+1.2 +2.0 +0.8 +1.8	Yes Yes Yes Yes
1012	Physical Emotional Control	Small change	Felt calmer/ more relaxed → increased confidence and control → increased activity	6	5	−1	Yes	3	3	0	No	Emotion: 5.0 Mastery: 5.3 Fatigue: 4.3 Dyspnea: 3.0	Emotion: 6.6 Mastery: 6.8 Fatigue: 5.8 Dyspnea: 5.0	+1.6 +1.5 +1.5 +2.0	Yes Yes Yes Yes
1013	Physical Emotional	No change	N/A	7	8	+1	No	4	5	+1	No	Emotion: 5.7 Mastery: 5.5 Fatigue: 5.3 Dyspnea: 2.4	Emotion: 5.7 Mastery: 5.3 Fatigue: 6.3 Dyspnea: 2.8	0 −0.2 +1.0 +0.4	No No Yes No
1014	Physical Emotional Social Control	Large change	Able to calm down quicker → breathe more easily → not panic → can do more	8	6	−2	Yes	6	4	−2	Yes	Emotion: 5.9 Mastery: 6.8 Fatigue: 5.3 Dyspnea: 1.6	Emotion: 6.6 Mastery: 6.5 Fatigue: 6.3 Dyspnea: 2.0	+0.7 −0.3 +1.0 +0.4	Yes No Yes No
1015	Physical Emotional Social Control	Large change	Felt calmer → breathing was easier → felt confident/ able to cope → physically do more	7	6	−1	Yes	4	4	0	No	Emotion: 3.7 Mastery: 4.3 Fatigue: 2.8 Dyspnea: 1.8	Emotion: 5.1 Mastery: 5.8 Fatigue: 3.8 Dyspnea: 2.4	+1.4 +1.5 +1.0 +0.6	Yes Yes Yes Yes
1016	Physical	No change	N/A	7	7	0	No	5	5	0	No	Emotion: 5.0 Mastery: 5.8 Fatigue: 3.3 Dyspnea: 3.6	Emotion: 4.6 Mastery: 4.8 Fatigue: 3.0 Dyspnea: [e]	−0.4 −1.0 −0.3 [e]	No No No [e]
1017	Physical Emotional Control	Small change	Breathing improved → felt more in control → able to do more	8	8	0	No	5	3	−2	Yes	Emotion: 5.3 Mastery: 5.0 Fatigue: 3.5 Dyspnea: 2.0	Emotion: 5.4 Mastery: 5.8 Fatigue: 3.3 Dyspnea: 2.6	+0.1 +0.8 −0.2 +0.6	No Yes No Yes
1018	Physical Emotional Social	No change	N/A	8	8	0	No	5	7	+2	No	Emotion: 4.3 Mastery: 3.8 Fatigue: 2.8 Dyspnea: 2.2	Emotion: 3.4 Mastery: 3.5 Fatigue: 2.5 Dyspnea: 2.4	−0.9 −0.3 −0.3 +0.2	No No No No
1019	Physical	No change	N/A	8	[e]	[e]	[e]	6	[e]	[e]	[e]	Emotion: 3.3 Mastery: 4.8 Fatigue: 2.5 Dyspnea: 1.2	Emotion: [e] Mastery: [e] Fatigue: [e] Dyspnea: [e]	[e] [e] [e] [e]	[e] [e] [e] [e]
1020	Physical Social Spiritual	No change	N/A	9	9	0	No	5	7	+2	No	Emotion: 5.4 Mastery: 5.5 Fatigue: 4.3 Dyspnea: 2.6	Emotion: 5.3 Mastery: 6.0 Fatigue: 4.0 Dyspnea: 2.6	−0.1 +0.5 −0.3 0	No Yes No No
1021	Physical Emotional Control	Small change	When breathing bad feeling less panicky	7	5	−2	Yes	4	3	−1	Yes	Emotion: 3.7 Mastery: 3.3 Fatigue: 4.3	Emotion: 4.6 Mastery: 5.5 Fatigue: 4.3	+0.9 +2.2 0	Yes Yes No

(*Continued*)

Table 2
Continued

ID	Qualitative (Important Domains)	Qualitative (Perceived Change)[a]	Qualitative Direction of Change	NRS (Worst), Range 0–10				NRS (Average), Range 0–10				CRQ (Domains), Range 1–7			
				BL	D28	Change Score	Clinically Important[b]	BL	D28	Change Score	Clinically important[c]	BL	D28	Change Score	Clinically Important[d]
			→ more in control → less anxious									Dyspnea: 2.2	Dyspnea: 3.0	+0.8	Yes
1022	Physical Emotional Control	Small change	Breathing better → feeling calmer → did not panic as much → more in control	10	7	−3	Yes	8	6	−2	Yes	Emotion: 2.9 Mastery: 2.8 Fatigue: 3.8 Dyspnea: 1.2	Emotion: 4.1 Mastery: 4.3 Fatigue: 4.0 Dyspnea: 2.2	+1.2 +1.5 +0.2 +1.0	Yes Yes No Yes

NRS = numerical rating scale; CRQ = Chronic Respiratory Questionnaire; BL = baseline; D28 = Day 28.
[a]Qualitative (perceived change) is the perceived change reported by participants during a qualitative interview.
[b]Clinically important improvement based on the minimal clinically important difference for the NRS (worst).
[c]Clinically important improvement based on the minimal clinically important difference for the NRS (average).
[d]Clinically important improvement based on the minimal clinically important difference for the CRQ.
[e]Missing data.

described how feeling calm resulted in easier breathing, and his outcome measure data showed a clinically important change in the CRQ emotion, and NRS worst and average.

It did something and it just helped me calm down a lot quicker than I normally would. I can calm down a lot quicker, so I can, I can breathe a lot easier. It helped me- something to me it just helped me relax so much and now I don- I don't panic anymore, you know.

Participant ID 1014

A female participant with clinically important changes in the NRS worst, CRQ emotion, and mastery domains described fewer episodes of panic and being able to cope better.

I seem as though I can cope better with it now as I say, you know, the panic, erm.

Participant ID 1015

Some participants described no change in their experience of breathlessness. This was also commonly captured in the quantitative outcome measures, and can be seen in the following examples. Both of these participants had no clinically important change in CRQ domains, or in NRS worst and average.

Perhaps find it that little bit easier to breathe. But unfortunately, it didn't happen for me.

Participant ID 1007

I just really didn't feel as though it made any difference

Participant ID 1020

Patterns of Change Across Domains

Where changes in experience were described, participants sometimes proposed a pattern of change, where a change in one domain was associated with a change in another. For some, improvements within the emotional domain were associated with improvements physically. The following two participants described feeling calmer and less frightened, and therefore being able to do more physically. Their outcome measure data showed clinically important changes in NRS worst, CRQ emotion, mastery, and fatigue.

Erm, I felt calmer. I felt as though I could do more, erm, er, I cou- yeah I could do more, because me breathing, obviously I'd settled that bit, yeah.

Participant ID 1015

It used to frighten me to get up because I thought, I'm not going to make it to the kitchen with the breathing, before I get (11.48), but now I can get up, go ahead and put the kettle on, make myself a cup of tea and I'm okay. Yeah, it's so, I-I-I am really glad that that I've done it.

Participant ID 1003

For some, a change in breathing led to improved confidence and a sense of feeling more in control. This increased confidence enabled participants to try to do more, a situation they might not have attempted in the past. This male participant with ILD described feeling more in control and therefore being able to do more. His outcome measure data showed a clinically important change in his CRQ mastery.

> *It didn't change my feelings, but, my breathing improved. Erm, stamina-wise and control-wise. And kind of, control-wise was that I, I didn't get out of breath as easy, I could do a bit more- not vast amounts, erm, but the breathing certainly was more comfortable.*
>
> Participant ID 1017

Another female participant with COPD described attempting to do things which she had previously avoided because she now felt she could do it, and was prepared to do it. Her outcome measure data showed a clinically important change in CRQ emotion and mastery, as well as in the NRS worst.

> *Well, I could do it, I could do it, and I was prepared to do it, but normally I just wouldn't dare to attempt doing it, cause I know how it would end up, yeah.*
>
> Participant ID 1015

Disagreement Between Patients' Experience and Outcome Measures

Sometimes, a perceived change in patients' experience of breathlessness was not captured by the quantitative outcome measures. One male participant with ILD described a slow gradual change in his breathing which he did not notice until finishing the trial and stopping the trial medication. Although there was no change in NRS worst scores, a clinically important change was captured in the NRS average and CRQ mastery or dyspnea.

> *Well I didn't recognise it at the time, but it did actually erm, improve my breathing. But, it was a noticeable improvement. When I came off the drug.*
>
> Participant ID 1017

Another participant perceived no change during the trial period, but his quantitative data suggested a clinically important change in NRS worst and CRQ. This participant described some difficulties completing scale-based outcome measures.

> *It was difficult to number, and whether, if I was getting any better or worse, it was difficult then to compare the last reading to this reading.*
>
> Participant ID 1005

Discussion

This study found that three commonly used measures (NRS average, NRS worst, and CRQ) captured the changes that participants reported in their qualitative experience. Agreement was highest with the NRS worst, which appeared to capture changes across multiple domains using the question "How bad has your breathlessness felt at its worst over the past 24 hours?" We know that patients' describe concerns relating to breathlessness across multiple domains,[6] and therefore when testing new treatments, it is important to capture change across these domains.

In this mixed-methods study, the NRS average (using the question "How bad has your breathlessness felt on average over the past 24 hours?") appeared to capture physical changes consistently, and participants with a clinically important change commonly described easier breathing and improved physical activity. In comparison, the NRS worst (using the question "How bad has your breathlessness felt at its worst over the past 24 hours?") appeared to capture changes more extensively across multiple domains including physical, emotional, spiritual, social, and control. It is therefore possible that the NRS worst is measuring more than one construct.

These findings suggest that it is important to consider how the statement/question used to accompany the NRS impacts on what is being measured. The NRS was originally validated with the statement "Indicate how much shortness of breath you are having right now."[18] The accompanying statement/question has evolved over time with studies increasingly reporting an assessment of average (NRS average) and worst (NRS worst) breathlessness over the past 24 hours (Appendix I).[20–31,41,42] Even the wording used to describe "worst breathlessness" varies, with one study asking participants "What is the worst your breathlessness has been over the last 24 hours?" and another using the statement "Indicate how much shortness of breath you are having at worst at rest over the last 24 hours."[20,23] Appendix I demonstrates the variability in breathlessness studies of accompanying rating statement/question, none of which to our knowledge have been formally validated. This is an important area for future research, as the accompanying statement/question potentially changes what is being measured.

It is interesting that there is an example in our data where a participant has reported a higher score for the NRS average than the NRS worst (Participant ID 1003, Day 28). This is in keeping with the peak-end rule where evaluation of an episode is determined by the most distressing and final moments of the experience.[43] The peak-end rule has previously been demonstrated in induced breathlessness, with recalled

breathlessness higher relative to concurrent breathlessness.[44] More recently, a study investigated the relevance of the peak-end rule when assessing breathlessness using "NRS now," "NRS average," and "NRS worst." The study demonstrated fallibility of the "NRS average," which was affected by current breathlessness.[21] This strengthens the argument that the "NRS worst" may be more appropriate than the "NRS average" as an outcome measure in breathlessness trials.

In this mixed-methods study, change in patients' experience in the qualitative data was captured in at least one domain of the CRQ for 15 participants. When a change was perceived in the qualitative data, a clinically important change score was most commonly seen in the emotion or mastery domain suggesting that these domains may be particularly important as part of the experience of breathlessness. In comparison, change in patients' experience was less commonly captured in the dyspnea domain. This study recruited people with a modified Medical Research Council dyspnea scale grade 3 or 4, therefore those most severely affected by breathlessness. The dyspnea domain of the CRQ asks participants to identify important activities, and score how short of breath the activity has made them. It is possible that for this group of participants, despite an improvement in their overall experience of breathlessness, the activities identified in the dyspnea domain continue to result in severe shortness of breath, and therefore the scores do not reflect a clinically important change.

The qualitative data in this mixed-methods study also offer insights into how the domains of total breathlessness may be linked. Participants described how improvements within the emotional domain were associated with changes physically, and they were able to do more. A similar concept of "total pain" was described by Cicely Saunders in 1964 when a patient reported "the pain began in my back, but now it seems that all of me is wrong".[45] The model shows that pain is the sum of all domains. In our study, one participant described how a change in one domain was associated with changes in other domains. In his qualitative interview, he said "Everything was so much better" (Participant ID 1003).

Mirtazapine is licensed for the treatment of depression with potential additional beneficial effects on anxiety, both of which are common in those experiencing chronic breathlessness.[46,47] In this study, it is possible that by treating an underlying anxiety or depressive disorder, mirtazapine had a beneficial effect on the emotional response to breathlessness. However, although not powered to detect an effect, results from this feasibility trial did not find a difference when controlling for anxiety and depression using the hospital anxiety and depression scale (personal communication Higginson et al. 2019); however, this will be formally investigated in a full-scale trial.

Although the NRS (average and worst) and CRQ appeared to capture change in experience of breathlessness in this trial, it is important to consider whether a similar effect would be seen when evaluating a treatment which is not expected to impact on anxiety. The breathing, thinking, and functioning model described by Spathis et al. demonstrates how inefficient breathing, feelings of anxiety, and muscle deconditioning are all interlinked and can perpetuate the experience of breathlessness.[48] By using this model, you can see how an improvement in someone's functional ability (function) may lead to improved confidence and less anxiety (thinking), and so a treatment which does not target anxiety may have a beneficial effect on it. We therefore consider that the NRS (average and worst) and CRQ are valid measures to use in other treatment studies which do not specifically target anxiety.

Strengths and Weaknesses

This mixed-methods study uniquely combines qualitative with quantitative data collected within a blinded randomized feasibility trial. The main researcher (NL) remained blinded during data collection and analysis, which is unusual and strengthens confidence in the findings by reducing the risk of bias.[38,39] However, although the qualitative data were in-depth, a single interview may not have been sufficient to fully capture perceived change during and after the trial.

The NRS (24 hours) and CRQ (two weeks) assess different periods. Although patient recall is considered the gold standard for assessing breathlessness,[40] research suggests that patients have difficulty remembering symptom levels beyond several days,[49] and therefore a longer recall period can result in reduced accuracy.[50] In addition, even mild cognitive impairment has been shown to influence patient recall of symptom intensity.[51] Participants in this study were assessed for cognitive impairment during screening, but no formal evaluation of cognitive function was performed and therefore mild cognitive impairment may have been present. The period between the trial ending and a qualitative interview being conducted also varied, and this may have increased the risk of recall bias in the qualitative interviews.

A single researcher undertook all interviews increasing the risk of interpretation bias, and some participants had met the researcher during the trial

period. Risks of bias were minimized by double coding a random subset of transcripts, discussion of findings within the research team, and use of a reflexive diary. The quantitative data were collected by designated researchers and research nurses at each site, and there may have been variability in how outcome measures were administered between sites and individuals, although this was minimized by training, and use of a data collection manual.

What This Study Adds

This study provides new evidence to support choice of primary outcome measure in clinical trials of interventions for chronic or refractory breathlessness. Choice of measure is key, but for some measures such as the NRS, the accompanying statement/question is perhaps the most important consideration. Although multiple domain measures are often considered most appropriate to measure complex symptoms like breathlessness, lengthy questionnaires can cause an increased burden for participants and can lead to missing data in clinical trials and research. In comparison, the NRS is short, self-administered, and simple to complete.

The results of this study suggest that the NRS worst using the question "How bad has your breathlessness felt at its worst over the past 24 hours?" is able to capture change in patients' experience of breathlessness across domains known to be important to patients.[6] It may therefore be an appropriate primary outcome measure in future breathlessness trials. However, it is important to acknowledge that validation work is first required to understand what constructs this question is measuring, and even whether individual constructs can be unpicked. These results also provide options to support the assessment and management of chronic or refractory breathlessness in clinical practice. For clinicians, where time constraints and wanting to minimize the burden to patients are key challenges, the NRS is an easily accessible outcome measure which could be integrated into routine clinical care. However, there may also be situations when a more detailed assessment is required to understand which particular domains of breathlessness are changing, and a multiple domain measure be most appropriate.

Conclusions

The changing experience of breathlessness during this trial was usually captured by the NRS worst, NRS average, and CRQ. Agreement was highest with the NRS worst, using the question "How bad has your breathlessness felt at its worst over the past 24 hours?" This study suggests that the NRS worst can capture important patient-reported changes in breathlessness, and therefore may be an appropriate measure in breathlessness trials. Future work should confirm the construct validity of the NRS worst using the rating question "How bad has your breathlessness felt at its worst over the past 24 hours?"

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The authors declare that they have no conflict of interest.

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Appendix

Appendix I
Wording of NRS Across Studies

Manuscript Title	Author/Year/Journal	NRS Wording
No detail on wording in manuscript		
Fan Therapy Is Effective in Relieving Dyspnea in Patients With Terminally Ill Cancer: A Parallel-Arm, Randomized Controlled Trial.	Kako J, 2018, JPSM.	**No detail on wording in manuscript**
Low-Dose Morphine for Dyspnea in Terminally Ill Patients with Idiopathic Interstitial Pneumonias.	Matsuda Y, 2017, Journal of Palliative Medicine.	**No detail on wording in manuscript**
The Effect of Using an Electric Fan on Dyspnea in Chinese Patients With Terminal Cancer.	Wong SL, 2017, Am J Hosp Palliat Care.	**No detail on wording in manuscript**
Inspiratory High Frequency Airway Oscillation Attenuates Resistive Loaded Dyspnea and Modulates Respiratory Function in Young Healthy Individuals.	Morris T, 2014, PLoS One.	**No detail on wording in manuscript**
Dyspnea scales in the assessment of illiterate patients with chronic obstructive pulmonary disease.	Martinez JA, 2000, Am J Med Sci.	**No detail on wording in manuscript**
Breathlessness now		
Validation of the Dyspnea Exertion Scale of Breathlessness in People With Life-Limiting Illness.	Sandberg J, 2018, JPSM.	How is your breathlessness right now?
Verbal numerical scales are as reliable and sensitive as visual analog scales for rating dyspnea in young and older subjects.	Morris NR, 2007, Respir Physiol Neurobiol.	How short of breath are you right now
Effect of Prophylactic Fentanyl Buccal Tablet on Episodic Exertional Dyspnea: A Pilot Double-Blind Randomized Controlled Trial.	Hui D, 2017, JPSM.	Dyspnea intensity now
Impact of Prophylactic Fentanyl Pectin Nasal Spray on Exercise-Induced Episodic Dyspnea in Cancer Patients: A Double-Blind, Randomized Controlled Trial.	Hui D, 2016, JPSM.	Dyspnea intensity "now"
Magnetoencephalography to investigate central perception of exercise-induced breathlessness in people with chronic lung disease: a feasibility pilot.	Johnson MJ, 2015 BMJ Open.	Breathlessness intensity "now," at maximal exertion, and then every minute during recovery.
Assessment of dyspnoea in the emergency department by numeric and visual scales: A pilot study.	Placido R, 2015, Anaesth Crit Care Pain Med.	Tell me on a scale of 0—10, what is the level of your shortness of breath. Zero is no shortness of breath and 10 is the worst possible shortness of breath you can possibly imagine.
Effects of prophylactic subcutaneous fentanyl on exercise-induced breakthrough dyspnea in cancer patients: a preliminary double-blind, randomized, controlled trial.	Hui D, 2014, JPSM.	Intensity of dyspnea "now"
High Flow Oxygen and Bilevel Positive Airway Pressure for Persistent Dyspnea in Patients With Advanced Cancer: A Phase II Randomized Trial.	Hui D, 2013, JPSM.	Intensity of dyspnea "now"
Proposing a standardized method for evaluating patient report of the intensity of dyspnea during exercise testing in COPD.	Hareendran A, 2012, Int J Chron Obstruct Pulmon Dis.	Participants asked to indicate how much shortness of breath they are having right now
Average and worst breathlessness		
Are within-person Numerical Rating Scale (NRS) ratings of breathlessness 'on average' valid in advanced disease for patients and for patients' informal carers?	Wade J, 2017, BMJ Open Respir Res.	What is the worst your breathlessness has been over the last 24 hours? How has your breathlessness been over the last 24 hours on average?

(*Continued*)

Appendix I
Continued

Manuscript Title	Author/Year/Journal	NRS Wording
Assessment of Breathlessness in Lung Cancer: Psychometric Properties of the Dyspnea-12 Questionnaire.	Tan JY, 2017, JPSM.	Average breathlessness Worst breathlessness Breathlessness-related unpleasantness Breathlessness-related distress patients' ability to cope with breathlessness
Practical Dyspnea Assessment: Relationship Between the 0–10 Numerical Rating Scale and the Four-Level Categorical Verbal Descriptor Scale of Dyspnea Intensity.	Wysham NG, 2015, JPSM.	How is your breathlessness right now? How has your breathlessness been over the last 24 hours, on average? What is the worst your breathlessness has been over the last 24 hours?
An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial.	Higginson IJ, 2014, The Lancet Respiratory Medicine.	Indicate how much shortness of breath you are having on average over the last 24 hours? At worst at rest over the last 24 hours? On exertion over the last 24 hours?
A randomised controlled trial of three or one breathing technique training sessions for breathlessness in people with malignant lung disease.	Johnson MJ, 2015, BMC Med.	Worst breathlessness over the previous 24 hours Average intensity of breathlessness over the past 24 hours Distress due to breathlessness Coping with breathlessness Satisfaction with care of breathlessness
Management of the respiratory distress symptom cluster in lung cancer: a randomised controlled feasibility trial.	Yorke J, 2015, Supportive Care in Cancer.	Average breathlessness in the past 24 hours Worst breathlessness in the past 24 hours Distress associated with breathlessness Unpleasantness associated with breathlessness Relief from breathlessness Ability to cope with breathlessness
Repeat dose opioids may be effective for breathlessness in chronic heart failure if given for long enough.	Oxberry SG, 2013, Journal of Palliative Medicine.	Average and worst breathlessness over the past 24 hours Distress, satisfaction, and coping with breathlessness
A randomised trial of high vs. low intensity training in breathing techniques for breathless patients with malignant lung disease: a feasibility study.	Barton R, 2010, Lung Cancer.	Perceived severity of breathlessness (average and worst over the past 24 hours, and "now") Distress caused by breathlessness Ability to cope with breathlessness
The effect of resistance inspiratory muscle training in the management of breathlessness in patients with thoracic malignancies: a feasibility randomised trial.	Molassiotis A, 2015, Support Care Cancer.	Perceived severity of breathlessness (average and "worst" over the past 24 hours, and "now") and distress caused by breathlessness Ability to cope with breathlessness
Minimally clinically important difference in chronic breathlessness: Every little helps.	Oxberry SG, 2012, Am Heart J.	Intensity of average breathlessness over the past 24 hours Worst breathlessness over the past 24 hours
Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial.	Oxberry SG, 2011, Eur J Heart Fail.	Severity of average breathlessness Worst breathlessness over the past 24 hours Breathlessness "now" Coping with breathlessness
Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial.	Abernethy AP, Lancet, 2010.	Breathlessness right now Average dyspnea in the past 24 hours Worst breathlessness in the past 24 hours Relief of dyspnea over the previous 24 hours
Average breathlessness		
Association of Descriptors of Breathlessness With Diagnosis and Self-Reported Severity of Breathlessness in Patients With Advanced Chronic Obstructive Pulmonary Disease or Cancer.	Chowienczyk S, 2016, JPSM.	How has your breathlessness been over the last 24 hours on average? How distressed are you by your breathlessness?

(*Continued*)

Appendix I
Continued

Manuscript Title	Author/Year/Journal	NRS Wording
Worst breathlessness and breathlessness now		
Predictors of response to corticosteroids for dyspnea in advanced cancer patients: a preliminary multicenter prospective observational study.	Mori M, 2017, Support Care Cancer.	Dyspnea worst Dyspnea now
Distress due to breathlessness		
Is a specialist breathlessness service more effective and cost-effective for patients with advanced cancer and their carers than standard care? Findings of a mixed-method randomised controlled trial.	Farquhar MC, 2014, BMC Med.	Patient distress due to breathlessness
The clinical and cost effectiveness of a Breathlessness Intervention Service for patients with advanced non-malignant disease and their informal carers: mixed findings of a mixed method randomised controlled trial.	Farquhar MC, 2016, Trials.	Patient distress due to breathlessness
Other		
Acupuncture for Dyspnea in Lung Cancer: Results of a Feasibility Trial.	Bauml J, 2016, Integr Cancer Ther.	Dyspnea severity in the past 7 days
Morphine in the management of dyspnoea in ALS. A pilot study.	Clemens KE, 2008, Eur J Neurol.	Intensity of dyspnea
Do the trajectories of dyspnea differ in prevalence and intensity by diagnosis at the end of life? A consecutive cohort study.	Currow DC, 2010, JPSM.	Intensity of dyspnea

NRS = numerical rating scale.

Appendix II

Full eligibility criteria

Inclusion criteria:

1. Male or female aged ≥18 years
2. Diagnosed with cancer, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), or chronic heart failure (New York Heart Association (NYHA) Class III or IV)
3. Breathlessness severity: modified MRC dyspnea scale grade 3 or 4
4. On optimal treatment of the underlying condition in the opinion of the identifying clinician
5. Management of the underlying condition has remained unchanged for the previous one week
6. Reversible causes of breathlessness optimally treated in the opinion of the identifying clinician
7. Expected prognosis of two months or more
8. If female and of childbearing potential agrees to use adequate contraception
9. Able to complete questionnaires and trial assessments
10. Able to provide written informed consent

Exclusion criteria:

1. Existing antidepressant use
2. Known contraindication to mirtazapine
3. Hypersensitivity to the active substance or to any of the components of the mirtazapine or placebo (e.g., lactose intolerance)
4. Australia modified Karnofsky Performance Scale ≤40
5. Pregnant or breast-feeding women
6. Patients with acute cardiac events within three months of randomization (myocardial infarction, unstable angina pectoris, or significant cardiac conduction disturbance)
7. Patients with known hepatic impairment
8. Patients with known renal impairment
9. Patients with uncontrolled blood pressure

10. Patients with uncontrolled diabetes mellitus
11. Patients with uncontrolled seizures, epilepsy, or organic brain syndrome
12. Patients with severe depression or suicidal thoughts
13. Patients with a history of psychotic illness (schizophrenia, bipolar disorder, mania, hypomania, or other psychotic disturbances)

Appendix III

Topic Guide

You have recently taken part in a study called Better B. I would like to talk to you to understand your experience of taking part, what you expected, and what it was like.

If you want to stop the interview at any point let me know. You do not need to give a reason, and your clinical care will not be affected. Everything you say will be kept confidential.

Do you have any questions before we begin?

Introduction/Better-B

What did you understand about the study?

What was your experience of taking part?

Prompt: Can you tell me a bit about that?

Recruitment/joining the study

How were you asked to take part in the study?

What was that like?

Prompt: Who spoke to you? What were you told? Where were you at the time?

What were your expectations?

Why did you decide to take part?

Prompt: What specifically did you want to see improved? What change were you hoping for?

Trial Processes/Taking Part

What did you understand about the treatment you received?

Prompt: What did you think about taking an antidepressant medication? What do you understand about a placebo drug/randomization?

How did you find taking the medication?

Probe: Did you have any difficulties? How did you manage with your other medications? (Dosette Box/Blister Pack/Diary as reminder).

How did you being visited at home?

Would you have preferred to have been seen somewhere else?

How did you find it completing the questionnaires?

Probe: What did you think about the questions we asked? Do you think they were the right questions? Did they capture what is important to you?

Would anything have made it easier to take part?

Probe: What were the downsides to taking part?

Change

Tell me in what ways the drug changed how you felt?

Prompt: Did you notice any change in your breathing, sleep, appetite, drowsiness?

What did you hope would change?

For you what would be the most important change?

Were there any changes you had not expected?

Closing Section

Is there anything else that you think is important for me to know?
Is there anything that has worried you during the course of this conversation?
Is there anything else you would like to talk about?

Appendix IV
Participant Demographics

Participant ID	Age, yrs	Diagnosis	Gender	Trial Completer/ Noncompleter
1001	84	ILD	Male	Completer
1002	70	COPD	Male	Completer
1003	68	COPD	Male	Completer
1004	71	COPD	Male	Completer
1005	76	ILD	Male	Completer
1006	71	HF	Male	Completer
1007	66	ILD	Male	Completer
1008	64	ILD	Male	Completer
1009	78	COPD	Male	Completer
1010	70	ILD	Female	Completer
1011	70	COPD	Female	Completer
1012	67	ILD	Male	Completer
1013	73	COPD	Male	Completer
1014	64	COPD	Male	Completer
1015	74	COPD	Female	Completer
1016	82	HF	Male	Non completer
1017	72	ILD	Male	Completer
1018	83	Cancer	Female	Completer
1019	74	ILD	Female	Non completer
1020	62	COPD	Male	Completer
1021	56	COPD	Female	Completer
1022	81	COPD	Male	Completer

ILD = interstitial lung disease; COPD = chronic obstructive pulmonary disease; HF = heart failure.

Appendix V
Thematic Coding Framework

Overarching Theme	Theme	Subtheme	Node
Change in experience of breathlessness	Physical	Relief of symptom	Easier breathing
			Improved appetite
			Able to eat more
			Improved sleeping
		Able to do more	More active
			Able to do activities of daily living more easily
		Perceived adverse effects of trial medication	Feeling sick
			Feeling drowsy
	Emotional	Sense of wellbeing	Feeling more relaxed
			Feeling calm
			Feeling more upbeat and positive
		Response to episodes of panic	Able to calm down more quickly
			Not feeling frightened
	Spiritual	Able to do more	Feeling positive about being able to contribute
			Sense of purpose
			Sense of satisfaction
		Wellbeing	Feeling positive
			Able to enjoy life
	Social	Able to go out more	Able to socialize
			Able to meet other people
			Feeling less isolated
			Able to enjoy activities
		Impact on relationships	Positive impact on close relationships
			Less reliant on others
	Control	Sense of control	During episode of breathlessness
			Less likely to restrict or avoid activities
		Increase in confidence	Able to be more independent
			Less reliant on others

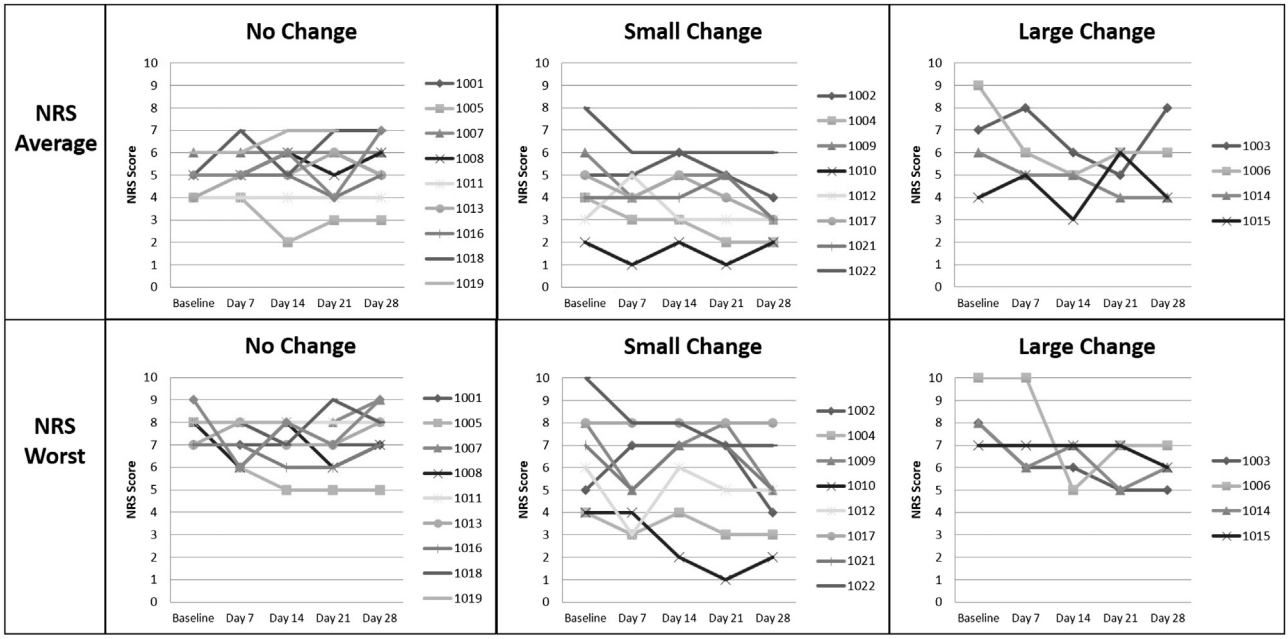
Appendix VI
Examples of Change in Experience Mapped Onto the Domains of "Total Breathlessness"

Experience Within Trial	Domain of Total Breathlessness	Participant Quote
The physical impact of breathlessness was prominent for all participants, and many hoped to see improvements in activity levels from taking the trial medication.	Physical	*It would be nice that I would actually be able to walk down the hill, as well as erm, you know, I, I used to be able to, I had a problem coming up the hill, but erm, now I have a problem walking down the hill as well.* Participant ID 1010
The emotional impact of breathlessness was also common with participants describing a repeated cycle of breathlessness and anxiety. Some participants reflected on whether a medication which enabled them to feel calmer could break this cycle.	Emotional	*You can get out of breath and then you can panic, cause you're not getting your breath and you're not breathing through your nose and letting it out through your mouth, you're sort of gasping.* Participant ID 1018
The physical and emotional effects caused distress in other aspects of participant's lives, commonly impacting on social and spiritual domains.	Social and Spiritual	*It turns you into a prisoner really, not being able to do anything, without getting shortness of breath.* Participant ID 1013
		I've been used to walking up mountains and, in the Lake District and erm, the Dales and I can't do any of that now. And er, it really does get me down that I can't do housework the same, gardening, everything. Participant ID 1015
Control and context were important across all domains. One participant described withdrawing from social activities for fear that an episode of breathlessness might occur. For another, the unpredictability of breathlessness left them feeling unable to make plans.	Context and Control	*Well, you, you're maybe struggling to breathe, and then you're getting yourself all hot and in a bother and then that sort of gets you churning in your stomach and then your chest seems to close up even more, and then you start sweating and all that type of thing, and I think, I was hoping that taking the, the medication would calm me down and it would be like 'right, relax, take a breath, everything's fine', and then I wouldn't be suffering those symptoms.* Participant ID 1021

(*Continued*)

Appendix VI
Continued

Experience Within Trial	Domain of Total Breathlessness	Participant Quote
		I can't plan going out, cause, from day-to-day you can think, oh we'll go this tomorrow, then you wake up tomorrow and you just cant do anything. So plans, you just don't plan anything, you go day-to-day and see how you are. Participant ID 1013



Appendix VII. NRS Change over time. NRS = numerical rating scale.