Mirtazapine to alleviate severe breathlessness in patients with COPD or interstitial lung diseases (BETTER-B): an international, multicentre, double-blind, randomised, placebo-controlled, phase 3 mixed-method trial

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Summary

Background Breathlessness frequently becomes severe among people with respiratory disease. Mirtazapine, a widely used antidepressant, has shown promise in the modulation of respiratory sensation and the response to it, as well as reducing feelings of panic, which often accompanies breathlessness. We aimed to determine the effectiveness of mirtazapine to alleviate severe persisting breathlessness.

Methods This international, multicentre, phase 3, parallel-group, double-blind, randomised, placebo-controlled trial across 16 centres in seven countries (Australia, Germany, Ireland, Italy, New Zealand, Poland, and the UK), recruited adults with chronic obstructive pulmonary disease (COPD), interstitial lung diseases, or both, and grade 3 or 4 of the modified Medical Research Council breathlessness scale. Consenting participants were randomly assigned (1:1) to receive oral mirtazapine or matching placebo for 56 days. Randomisation was by minimisation. The initial mirtazapine dose was 15 mg, escalating to a maximum of 45 mg per day, tapered at treatment end. Participants, caregivers, assessors, and investigators were masked to group assignment. The primary outcome was worst breathlessness in the preceding 24 h measured on a 0–10 numerical rating scale (NRS), at 56 days post-treatment start, with follow-up to 180 days. The primary analysis was performed in the modified intention-to-treat population using multivariable multi-level repeated measures model. This trial was registered with ISRCTN (ISRCTN10487976 and ISRCTN15751764 [Australia and New Zealand]) and EudraCT (2019–002001–21) and is complete.

Findings Between Feb 4, 2021 and March 28, 2023, we enrolled 225 eligible participants (148 men and 77 women, 113 to the mirtazapine group and 112 to the placebo group). The median age was 74 years (IQR 67–78). No evidence of a difference was found in worst breathlessness at day 56 between mirtazapine and placebo (difference in adjusted mean NRS score was 0·105 [95% CI –0·407 to 0·618]; p=0·69). Although the study was underpowered, the primary endpoint effect did not reach the pre-specified treatment effect of 0·55 for worst breathlessness score reduction that the study was powered to detect for the primary analysis. There were 215 adverse reactions in 72 (64%) of 113 participants in the mirtazapine group versus 116 in 44 (40%) of 110 participants in the placebo group; 11 serious adverse events in six (5%) participants in the mirtazapine group versus eight in seven (6%) participants in the placebo group; and one (1%) suspected unexpected serious adverse reaction in the mirtazapine group. At day 56, there were three deaths in the mirtazapine group and two deaths in the placebo group. At day 180, there were seven deaths in the mirtazapine group and 11 deaths in the placebo group.

Interpretation Our findings suggested that mirtazapine of doses 15 to 45 mg daily over 56 days does not improve severe breathlessness among patients with COPD or interstitial lung diseases and might cause adverse reactions. Based on these findings, we do not recommend mirtazapine as a treatment to alleviate severe breathlessness.

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Introduction

Chronic respiratory diseases cause a substantial burden, affecting 454·6 million people worldwide, with numbers predicted to increase.[1,2] Chronic obstructive pulmonary disease (COPD) is the most prevalent of these (affecting 212·3 million people); interstitial lung diseases affect a

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See Online for appendix

Research in context

Evidence before this study

Chronic obstructive pulmonary disease (COPD) and interstitial lung diseases are prevalent, affecting more than 217 million people globally, with associated breathlessness posing significant clinical and personal challenges. Despite this, effective treatment options are scarce, particularly in advanced disease stages. Our PubMed search from inception up to May 20, 2024, for clinical trials used the following terms: ("clinical" or "randomised trial") and ("breathlessness" or "dyspnoea" or "dyspnea") and ("COPD" or "emphysema" or "restrictive lung disease" or "lung fibrosis" or "interstitial lung diseases" or "interstitial pulmonary disease" or "respiratory") and ("antidepressant" or "mirtazapine"). No language restrictions were applied. Following a feasibility study, one trial (80% power) found no effect of sertraline on chronic breathlessness, randomising 223 participants, 71% with COPD, the rest with other causes, including restrictive lung disease and cancers; with a modified Medical Research Council (mMRC) breathlessness score of 2 or more. A trial of 26 participants with COPD tested 20 mg daily protriptyline. Case series and case report evidence is available for mirtazapine, along with the BETTER-B-feasibility study that informed the methods of this main trial. These trials lacked data for health or informal care use. Additionally, 24 other articles comprised study protocols of the above-mentioned studies, editorials, trials in depression, and practice or case reports.

Added value of the study

This study represents the first comprehensive evaluation of mirtazapine's effectiveness, safety, and health-care use in managing severe chronic breathlessness in patients with COPD or interstitial lung diseases. To our knowledge, it is the largest trial targeting individuals most severely affected by breathlessness (mMRC score ≥3), with broad generalisability across diverse populations and settings. It incorporated care use and qualitative data, providing a holistic picture. Despite our initial hypothesis, mirtazapine, administered at doses of 15 to 45 mg over 56 days, did not demonstrate statistically significant benefits versus placebo. Although the trial did not reach its target sample size, the results of the primary endpoint analysis did not find any benefit of mirtazapine, and it is unlikely that continuing recruitment would change this result. These findings were consistent across secondary outcomes. More adverse events were reported with mirtazapine use than placebo. Further analysis revealed that compared with the placebo group, individuals receiving mirtazapine had nearly double the number of nights in acute hospitals, plus higher mean rates of hospital use and informal caregiver support hours. Patient qualitative reports were consistent with these findings.

Implications of all the available evidence

Amalgamating results from this largest trial of mirtazapine, plus the sertraline and protriptyline trials, suggests that these antidepressants do not currently warrant recommendation for managing breathlessness in respiratory diseases. Mirtazapine exhibited no discernible benefit and possibly heightened adverse outcomes and health-care use. These results underscore the urgency for rigorous pragmatic clinical trials in assessing potential treatments for severe breathlessness, ensuring not only efficacy but also safety and lessened health-care burden. Clinicians and guidelines should avoid recommending untested treatments outside of a rigorous evaluation framework. The imperative for developing safe, efficacious treatments for severe breathlessness in respiratory diseases remains paramount.

further 4·7 million people.[1] In respiratory diseases, breathlessness is common, occurring in up to 90% of people with more advanced diseases, and affecting more than 75 million people worldwide.[3,4] As the 2024 GOLD report highlights, breathlessness worsens as disease progresses and is one of the most common, burdensome, and clinically challenging symptoms affecting patients with advanced respiratory disease in all settings.[5] Severe breathlessness has a devastating impact, greatly limiting a person's quality of life and that of their family, friends, and caregivers.[6] It results in high health, social, and informal care costs and is one of the most frequent causes of emergency hospital attendance.[7,8]

Despite the prevalence of chronic respiratory diseases, there is a paucity of effective treatments for persisting breathlessness, revealing a substantial gap in our therapeutic armamentarium.[5] The treatment of breathlessness in clinical practice varies widely across specialties and countries, even for patients with similar presenting features.[9] New therapies are urgently needed; there are currently no licensed medicines for chronic and refractory breathlessness globally, apart from regular, low-dose, sustained-release morphine in Australia.[10] The use of morphine to treat breathlessness is supported by weak evidence showing a small effect.[11]

Breathlessness is a distressing, multidimensional sensation resulting from complex interactions between physiological, environmental, cultural, and social factors.[5] Breathlessness sensations are closely linked to respiratory effort, suggesting shared neurophysiological origins.[12] Although COPD and interstitial lung diseases differ in their underlying processes, both conditions exhibit substantial respiratory mechanical impairments, exacerbating breathlessness.[13] Research across obstructive and restrictive lung diseases indicates a strong correlation between breathlessness intensity and neural respiratory drive, stemming from impaired respiratory mechanics.[14] In this situation, breathlessness can be relieved through targeting primary disease

processes to improve respiratory mechanics, reducing respiratory muscle workload, or modulating respiratory sensation processing in the brain.

Research suggests that antidepressants might modulate respiratory sensation and the response to it, even in the absence of a mood disorder, by enhancing levels of neurotransmitters (eg, serotonin) in respiratory control and other centres (eg, the amygdala).[15,16] The antidepressant mirtazapine also reduces feelings of panic. Panic often accompanies episodes of severe breathlessness.[15] Antidepressants might be an attractive option for clinicians and patients; they are already well studied in populations with advanced respiratory disease and those needing palliative care, are widely available, economical, and easy to implement for health systems, and have already been studied in neuropathic pain management.[17] Although there are case reports of the effectiveness, biological plausibility, and feasibility of antidepressants for treating breathlessness,[18] phase 3 trials are lacking. The BETTER-B trial aimed to assess the effectiveness of a new potential treatment, mirtazapine, for the reduction of self-reported breathlessness in people with COPD or interstitial lung diseases and severe breathlessness. The primary objective was to determine whether mirtazapine is an effective treatment for the reduction of self-reported worst breathlessness over the past 24 h measured at day 56 post-start of treatment compared with placebo. Secondary objectives included assessing quality of life, health-care use, and patient and carer qualitative reports.

Methods

Study design and participants

BETTER-B was an international, multicentre, phase 3, parallel-group, double-blind, randomised, placebo-controlled pragmatic trial, with qualitative and health economic components, conducted in 16 centres in Australia, Germany, Ireland, Italy, New Zealand, Poland, and the UK. Our methods were informed by a feasibility trial.[18] We report our methods and results consistent with the CONSORT statement, pragmatic trial extension.[19]

Eligible participants were aged 18 years or older, with COPD, interstitial lung diseases, or both, and grade 3 or 4 of the modified Medical Research Council (mMRC) breathlessness scale, stable for the previous 2 weeks and on optimal treatment for reversible causes of breathlessness as judged by the referring clinician and according to best clinical guidance. Exclusion criteria included existing antidepressant use or other serotonergic active substances (eg, linezolid or St John's wort), known contraindications to mirtazapine, or an Australia-modified Karnofsky Performance Scale score of 40 or less (in bed more than 50% of the time) due to the likely shorter prognosis and inability to complete the 56 days post-start of treatment (for full details see the protocol, appendix pp 42–176). At each site, after training and initiation, the site principal investigator assumed overall responsibility for identifying and obtaining informed consent from participants at their respective sites. Potential participants were typically identified by nurses or other clinicians through outpatient and inpatient services (including respiratory, medical, rehabilitation, and palliative care clinics), community services, and review of clinical databases. Following this initial identification, potential participants underwent screening and were asked to provide written informed consent by principal investigators or their trained and authorised study delegates. Consenting participants were asked to identify the person closest to them, usually a family member or carer, who was also approached to consent to data collection.

The trial protocol, the written informed consent form, and other materials related to the participants were approved by the ethics committee at each sites. The trial was co-sponsored by King's College London (London, UK) and University College Dublin (Dublin, Ireland) and by University of Technology (Sydney, Australia) and was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. There were two protocol deviations (failures to dose escalate) and 22 violations (appendix p 40). The trial was registered with ISRCTN (ISRCTN10487976 and ISRCTN15751764 [Australia and New Zealand]) and EudraCT (2019–002001–21).

Randomisation and masking

All enrolled participants were randomly assigned (1:1) to receive either mirtazapine or matching placebo daily for 56 days, with dose escalation and tapering if indicated. After baseline data collection and entry onto the database, the Leeds Clinical Trial Research Unit performed all randomisation centrally by minimisation incorporating a random element (80%) to balance disease (COPD *vs* interstitial lung diseases), hospital anxiety and depression scale scores (≤10 *vs* >10), receiving opioids (yes *vs* no), and recruiting site.

Participants, caregivers, assessors, and investigators were masked to group assignment. The mirtazapine and placebo tablets were centrally manufactured to be identical in appearance; containers were labelled with unique 5-digit kit-codes to maintain the blinding. An unblinded statistician, independent of the trial, undertook activities requiring knowledge of the treatment group allocation. To maintain trial oversight, the supervising statistician was also unblinded to treatment group allocation throughout the trial. The sponsor's Clinical Trials Office regularly undertook inspections and no risk of unblinding was found.

Procedures

For participants assigned to receive mirtazapine, the daily dose was 15 mg (one tablet orally) for the first 14 days. For participants assigned to receive placebo, the daily dose was one placebo tablet orally for the first

14 days. There were two assessments for dose escalation (at days 14 and 28 post-start of treatment). These assessments were undertaken double blind in both study groups. If there was no improvement in patient reported breathlessness severity, measured using the Numerical Rating Scale (NRS; reported "at its worst" over the previous 24 h, with higher scores indicating more severe breathlessness), by 1 point or more compared with baseline NRS, and the drug had been well tolerated and adhered to, the daily dose of treatment was increased at day 14 by 15 mg per day to 30 mg per day (double dose), and at day 28 by 15 mg per day to 30 mg per day or 45 mg per day (depending on the current dose level). At the end of day 56 post-start of treatment (and where appropriate) the participants dose was tapered and discontinued.

Participant assessments were at baseline and at days 7, 14, 28, and 56 post-start of treatment. Participants were followed up 7 days after completing trial treatment (including dose tapering) to assess safety and toxicity of treatment, and then at 180 days post-start of treatment by phone, video call, or post to complete the final participant reported questionnaires.

Caregiver assessments took place at baseline and at days 28 and 56, with a follow-up postal assessment (or telephone or video call) at day 180 to complete the final questionnaires.

Where possible we used study questionnaires and materials already available and validated in other languages. Where these were not available, and for the Participant Information Sheet, consent form, patient diary, and GP or family doctor letters, forward and backward translations were done.

Patient and public involvement and engagement were integrated at all stages of planning, protocol development, and trial monitoring and delivery, through a specific BETTER-B patient and public involvement and engagement group and partnership with the European Lung Foundation. In addition, an ethics advisory board oversaw the programme of work, in addition to the usual trial steering and data quality and safety groups.

Outcomes

The specific details regarding the safety and effectiveness analyses were prespecified in the statistical analysis plan (version 2.0, approved July 3, 2023), before the final data lock.

The primary outcome was defined as self-reported worst breathlessness over the previous 24 h at 56 days post-start of treatment, recorded on a 0–10 NRS (from 0="Not breathless at all" to 10="The worst possible breathlessness").[20]

Secondary outcomes included worst breathlessness at other time points, average breathlessness, the number and duration of breathlessness episodes,[21] physical and emotional aspects of breathlessness (dyspnoea, fatigue, emotional function, and how quality of life is affected by a feeling of control over breathlessness) as assessed by the chronic respiratory questionnaire,[22] symptoms and concerns as assessed by the integrated palliative care outcome scale, subscales (physical symptoms, emotional symptoms, and communication or practical issues; each analysed individually as separate endpoints and in total),[23] anxiety and depression as assessed by the hospital anxiety and depression scale,[24] caregiver self-assessed burden according to the Zarit Burden Interview,[25] and caregiver assessment of patient breathlessness and other symptoms (further details are in the protocol, appendix pp 107–113). The full list of secondary endpoints assessed are in the protocol (appendix pp 111–113). All primary and secondary outcomes used the best validated versions in patients' native languages according to country of recruitment; all were piloted before use.

The safety endpoints were adverse reactions, serious adverse events, suspected unexpected serious adverse reactions, and deaths up to 180 days after treatment commenced.

We collected health-care use by participants using a bespoke adaptation of the Client Service Receipt Inventory used in similar trials.[26] This asks about both categories of formal care (eg, inpatient hospital admissions and outpatient services) and unpaid assistance from informal (eg, family) caregivers with basic and instrumental activities of daily living. We recorded use in the previous month at days 28 and 56 and calculated total use from baseline to total endpoint by summing these responses.

In two centres, one in Italy and one in the UK (because these countries had sufficient qualitative expertise to supervise and analyse in the local languages), consenting trial participants were approached for a qualitative sub-study to explore the treatment's perceived effects and side-effects, using open-ended questions following a topic guide. Interviews were conducted and transcribed in the native language and analysed in English using framework analysis.[27]

Statistical analysis

Primary and sensitivity analyses of the primary endpoint were conducted on the modified intention-to-treat analysis population, defined as randomly assigned participants who received at least one dose of trial treatment. For the primary analysis, a multivariable, multi-level repeated measures model was fitted to the NRS worst breathlessness score at days 7, 14, 28, and 56 post-start of treatment, with covariates for minimisation factors, baseline NRS score, time, treatment group, and corresponding treatment group-by-time; random effects for participant and participant-by-time interaction were included in the model. Contrast for the treatment effect at day 56, corresponding 95% CI, and significance are reported.

Missing data were imputed using multiple imputation by chained equations (50 imputations), assuming missing data were missing at random;[28] in addition to the stratification factors, baseline mMRC grade and long-term

oxygen therapy were included in the imputation model as auxiliary variables. Results across imputed data sets were combined using Rubin's rules.[29]

A sensitivity analysis of the primary endpoint assumed missing data were missing not at random. Data missing due to illness or death, according to the MORECare classification,[30] were explored and then imputed with NRS=10 (corresponding to worst possible breathlessness). The same multivariable multi-level repeated measures model as for the primary analysis was then fitted.

When analysing health-care use, we focused on hospital attendance and informal care, because these account for 70–80% of total health-care resource use in seriously ill populations.[31] Acute inpatient emergency admissions are sometimes avoidable in this population, but there can be substitution effects in which lower hospital care is associated with higher informal care use. Therefore, we analysed three measures of hospital care use (total inpatient days in acute hospital, total emergency department admissions, and total outpatient appointments) and one measure of informal care (total hours of informal unpaid care) from baseline to the primary endpoint at day 56. In keeping with the clinical outcomes analyses, to account for missing data due to non-response or attrition, we used multiple imputation with additional predictors to account for the determinants of utilisation data: age, sex, Charlson Comorbidity Index score, country of recruitment, and baseline use of the relevant outcome. To account for skewed outcomes, we used bootstrapping with 1000 replications for each of the 50 imputed datasets, combining estimates using Rubin's rules.[29] SAS version 9.4 was used to conduct the statistical analysis.

324 participants were required to provide 80% power for detecting a treatment effect of 0·55 on the primary outcome, worst breathlessness over the past 24 h. This effect size was agreed based on published estimates that the absolute reduction of 5·5 mm on a visual analogue scale, (ie, 0·55 on NRS), equated to a small effect of improvement reported by patients.[32] This corresponds to a small standardised effect size (0·25). This effect mirrors, and in some analyses surpasses, the effect sizes documented for opioids in alleviating refractory or severe breathlessness, as reported in Cochrane systematic reviews.[11] We assumed standard deviation of 1·52, two-group *t*-test of equal means, and two-sided 5% significance level and 25% attrition based on feasibility trial results.[18]

Role of the funding source

The funders of the study had no role in the data collection, analysis, interpretation, writing of the manuscript, or the decision to submit for publication.

Results

Between Feb 4, 2021 and March 28, 2023, 2499 participants were screened for eligibility, of whom 1919 (77%) were ineligible. The main reasons for ineligibility included

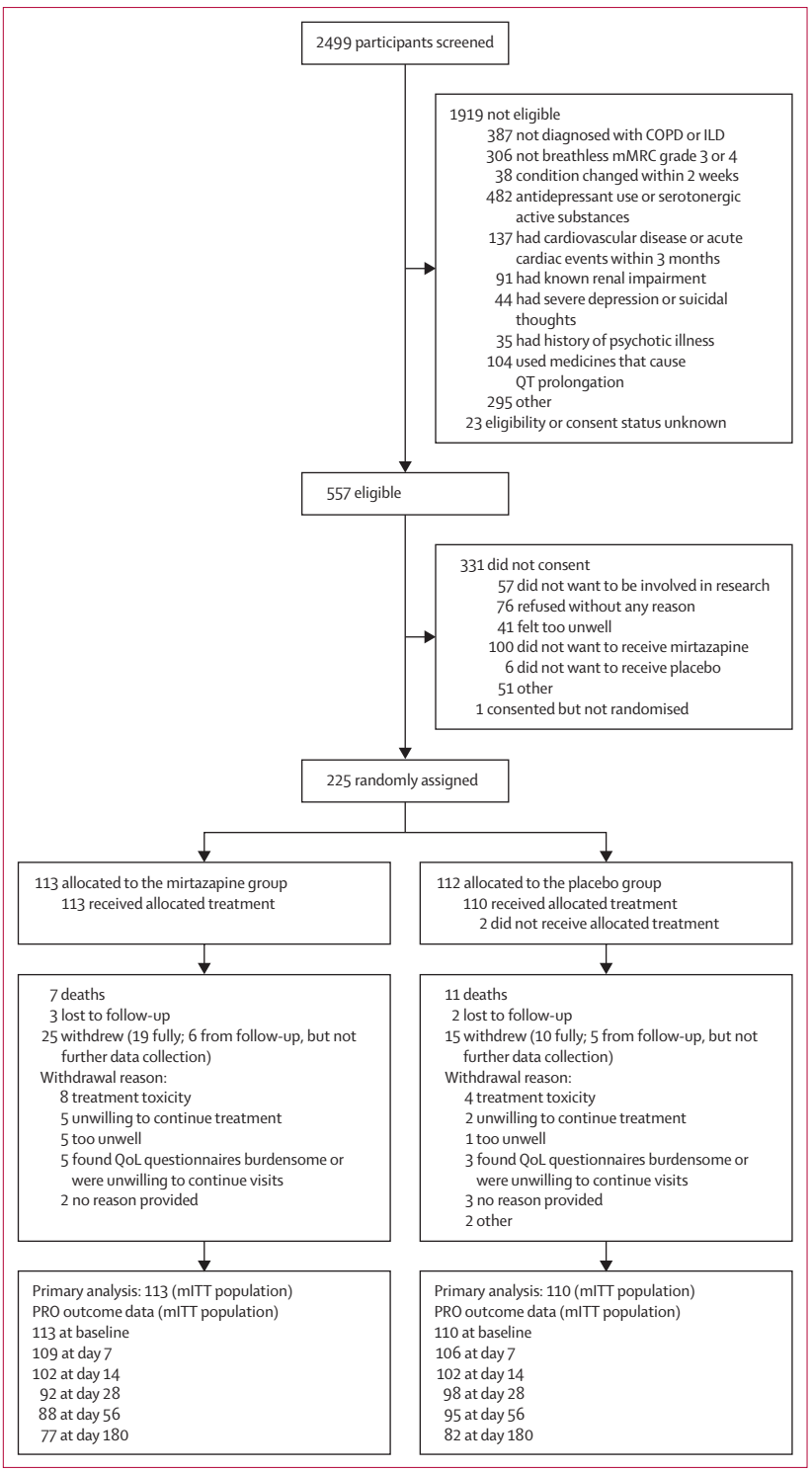

Figure 1: **Trial profile**
COPD=chronic obstructive pulmonary disease. ILD=interstitial lung diseases. mITT=modified intention-to-treat population. mMRC=modified Medical Research Council breathlessness scale. PRO=patient reported outcome. QoL=quality of life.

	Mirtazapine (n=113)	Placebo (n=112)	Total (n=225)
Age, years	74·0 (67·0–78·0)	73·0 (66·0–78·0)	74·0 (67·0–78·0)
Gender			
Male	73 (65%)	75 (67%)	148 (66%)
Female	40 (35%)	37 (33%)	77 (34%)
Ethnicity or origin*			
Europe (without Germany) (n=169)			
White—White British	46 (41%)	48 (43%)	94 (42%)
White—Irish	12 (11%)	10 (9%)	22 (10%)
White—Italian	16 (14%)	12 (11%)	28 (12%)
White—Slavic	2 (2%)	0	2 (1%)
White—Other†	6 (5%)	11 (10%)	17 (8%)
Black/African/Caribbean—Caribbean	0	1 (1%)	1 (<1%)
Black/African/Caribbean—Other	1 (1%)	0	1 (<1%)
Asian—Indian	2 (2%)	1 (1%)	3 (1%)
Other ethnic group—Don't know	1 (1%)	0	1 (<1%)
Germany (n=36)			
German	17 (15%)	18 (16%)	35 (16%)
Other	1 (1%)	0	1 (<1%)
Australia (n=10)			
Oceanian (Australia and New Zealand)	4 (4%)	2 (2%)	6 (3%)
Northwest European	0	2 (2%)	2 (1%)
Southern and Eastern European	0	2 (2%)	2 (1%)
New Zealand (n=10)			
New Zealand European	4 (4%)	4 (4%)	8 (4%)
Maori	1 (1%)	0	1 (<1%)
Indian	0	1 (1%)	1 (<1%)
Primary diagnosis			
COPD	63 (56%)	61 (55%)	124 (55%)
ILD	50 (44%)	51 (46%)	101 (45%)
HADS anxiety score			
≤10	89 (79%)	88 (79%)	177 (79%)
>10	24 (21%)	24 (21%)	48 (21%)
HADS depression score			
≤10	88 (78%)	88 (79%)	176 (78%)
>10	25 (22%)	24 (21%)	49 (22%)
Taking opioids			
Yes	19 (17%)	17 (15%)	36 (16%)
No	94 (83%)	95 (85%)	189 (84%)
mMRC grade			
Grade 3	75 (66%)	74 (66%)	149 (66%)
Grade 4	38 (34%)	38 (34%)	76 (34%)
Comorbidities			
Yes	95 (84%)	86 (77%)	181 (80%)
No	18 (16%)	26 (23%)	44 (20%)
Charlson index summary score	1·8 (1·3)	1·6 (1·1)	1·7 (1·2)
Integrated Palliative Care Outcome Scale total score	20·8 (9·1)	21·1 (9·7)	20·9 (9·4)
Chronic Respiratory Questionnaire emotional score (7 items)	30·9 (8·6)	30·8 (8·5)	30·8 (8·5)

Data are median (IQR), n (%), or mean (SD). COPD=chronic obstructive pulmonary disease. HADS=hospital anxiety and depression scale. ILD=interstitial lung diseases. mMRC=Modified Medical Research Council. *Ethnicity was self-reported by respondents and differs for regions due to variations in regional classifications. †Includes the 15 participants at the Polish site, "White—Other" was recorded for 13 participants, and "White—Other Polish" for two participants.

Table 1: **Baseline characteristics**

current antidepressant or serotonergic active substance use (482/1919 [25%]), not diagnosed with COPD or interstitial lung diseases (387 [20%]), and an mMRC breathlessness score less than 3 (306 [16%]; see figure 1 for the full list). The eligibility or consent status was unknown for 23 (1%) of 2499 screened participants, who were therefore excluded. There were 557 (22%) of 2499 potentially eligible participants; 331 (59%) of 557 participants did not consent, with the main reasons being not wanting to receive mirtazapine (100 [30%] of 331) or not wanting to be involved in research (57 [17%] of 331), and 76 (23%) of 331 participants declined without providing a reason. Extreme difficulty in recruiting participants during the COVID-19 pandemic (which meant the study had to pause in several sites, as respiratory clinicians had to focus on COVID-19 clinical care and research trials, with non-COVID-19 research being deprioritised) and the withdrawal of the UK from the EU (engendering delays and increased complexity in approvals) resulted in a smaller sample size than originally planned.

Of the 2499 participants screened, 225 (9%) were enrolled and randomly assigned: 113 to mirtazapine and 112 to placebo (figure 1). In addition, 75 caregivers of participants were eligible and consented: 43 from the mirtazapine group and 32 from the placebo group (appendix p 5).

All 113 participants in the mirtazapine group received the allocated treatment; 110 (98%) of 112 participants in the placebo group received the allocated treatment. Dose escalations occurred similarly across study groups. At day 14, 48% of participants receiving mirtazapine had escalation, compared with 53% of participants receiving placebo. At day 28, 35% of participants receiving mirtazapine had escalation, compared with 36% of participants receiving placebo. For more detailed information, see appendix p 15. At day 56, there were three deaths in the mirtazapine group and two deaths in the placebo group. The number of people who died by day 180 was: seven (6%) of 113 in the mirtazapine group and 11 (10%) of 112 in the placebo group. Five participants were lost to follow-up, three (3%) participants in the mirtazapine group and two (2%) in the placebo group. 25 (22%) participants in the mirtazapine and 15 (13%) participants in the placebo group withdrew by day 180.

Demographic and clinical characteristics were generalisable to the target population (table 1; appendix pp 6–9). The median age was 74 years (IQR 67–78), 73 (65%) of 113 participants in the mirtazapine group and 75 (67%) of 112 participants in the placebo group were men, most participants were recruited from hospital outpatients (mirtazapine: 86 [76%] of 113; placebo: 86 [77%] of 112), with an mMRC score of 3 (mirtazapine: 75 [66%]; placebo: 74 [66%]) or 4 (mirtazapine: 38 [34%]; placebo: 38 [34%]); 95 (84%) in the

	Mirtazapine (n=113)	Placebo (n=110)	Total (n=223)
Day 7			
Worst breathlessness (NRS) score collected	109 (97%)	106 (96%)	215 (96%)
Missed questionnaire	1 (1%)	0	1 (<1%)
Attrition due to illness	2 (2%)	1 (1%)	3 (1%)
Attrition at random	1 (1%)	3 (3%)	4 (2%)
Reason for attrition at random			
Unwilling to continue treatment	0	1/3 (33%)	1/4 (25%)
Withdrawal, no reason given	0	1/3 (33%)	1/4 (25%)
Physician advised to cease trial medication	0	1/3 (33%)	1/4 (25%)
Unwilling to continue visits	1/1 (100%)	0	1/4 (25%)
Day 14			
Worst breathlessness (NRS) score collected	103 (91%)	102 (93%)	205 (92%)
Missed questionnaire	3 (3%)	1 (1%)	4 (2%)
Attrition due to illness	3 (3%)	4 (4%)	7 (3%)
Attrition at random	4 (4%)	3 (3%)	7 (3%)
Reason for attrition at random			
Unwilling to continue treatment	1/4 (25%)	1/3 (33%)	2/7 (29%)
Withdrawal, no reason given	0	1/3 (33%)	1/7 (14%)
Physician advised to cease trial medication	0	1/3 (33%)	1/7 (14%)
QoL burdensome	1/4 (25%)	0	1/7 (14%)
Unwilling to continue visits	1/4 (25%)	0	1/7 (14%)
No further information	1/4 (25%)	0	1/7 (14%)
Day 28			
Worst breathlessness (NRS) score collected	93 (82%)	99 (90%)	192 (86%)
Missed questionnaire	3 (3%)	1 (1%)	4 (2%)
Attrition due to death	3 (3%)	0	3 (1%)
Attrition due to illness	8 (7%)	6 (6%)	14 (6%)
Attrition at random	6 (5%)	4 (4%)	10 (5%)
Reason for attrition at random			
Unwilling to continue treatment	2/6 (33%)	1/4 (25%)	3/10 (30%)
Withdrawal, no reason given	0	1/4 (25%)	1/10 (10%)
Physician advised to cease trial medication	0	1/4 (25%)	1/10 (10%)
Lack of efficacy	0	1/4 (25%)	1/10 (10%)
QoL burdensome	1/6 (17%)	0	1/10 (10%)
Unwilling to continue visits	1/6 (17%)	0	1/10 (10%)
No further information	2/6 (33%)	0	2/10 (20%)
Day 56			
Worst breathlessness (NRS) score collected	88 (78%)	93 (85%)	181 (81%)
Missed questionnaire	2 (2%)	3 (3%)	5 (2%)
Attrition due to death	3 (3%)	1 (1%)	4 (2%)
Attrition due to illness	12 (11%)	6 (6%)	18 (8%)
Attrition at random	8 (7%)	7 (6%)	15 (7%)
Reason for attrition at random			
Unwilling to continue treatment	3/8 (38%)	1/7 (14%)	4/15 (27%)
Participant choice	0	1/7 (14%)	1/15 (7%)
Withdrawal, no reason given	1/8 (13%)	1/7 (14%)	2/15 (13%)
Physician advised to cease trial medication	0	1/7 (14%)	1/15 (7%)
Lack of efficacy	0	1/7 (14%)	1/15 (7%)
QoL burdensome	1/8 (13%)	0	1/15 (7%)
Unwilling to continue visits	1/8 (13%)	0	1/15 (7%)
No further information	2/8 (25%)	2/7 (29%)	4/15 (27%)

MOREcare classification used. Missed questionnaire indicates that the participant completed questionnaires at later timepoints (ie, missingness is not due to attrition). One participant in the placebo group with reason for attrition due to illness then died (before day 56). QoL=quality of life.

Table 2: **Attrition**

mirtazapine group and 86 (77%) in the placebo group had comorbidities, and the median integrated palliative care outcome scale physical subscale (total of 10 symptoms) was 11·0 (IQR 8·0–15·0) in the mirtazapine group and 11·0 (7·0–16·0) in the placebo group.

Missing data patterns were different between treatment groups, with greater attrition due to illness or death in the mirtazapine group compared with the placebo group (table 2).

For the primary analysis on the primary endpoint, there was no evidence of a difference in worst breathlessness (NRS) score at day 56 between mirtazapine and placebo (223 participants included in the analysis [113 mirtazapine, 110 placebo]; difference in adjusted mean NRS score [mirtazapine minus placebo] was 0·105 [95% CI –0·407 to 0·618]; p=0·69; figure 2).

The sensitivity analysis conducted on the primary endpoint (to assess the impact of the variance in missing data patterns, under the assumption that missing data were not randomly distributed) supported the primary analysis. There was no evidence of a difference between treatment groups; the estimate of the difference in adjusted mean NRS score, (mirtazapine minus placebo) was 0·232 (95% CI –0·308 to 0·773; p=0·40). Secondary outcomes showed no apparent differences between groups for other measures of breathlessness, for overall palliative symptoms as measured by the integrated palliative care outcome scale, average NRS breathlessness score, chronic respiratory questionnaire subscales, integrated palliative care outcome subscales, anxiety and depression as

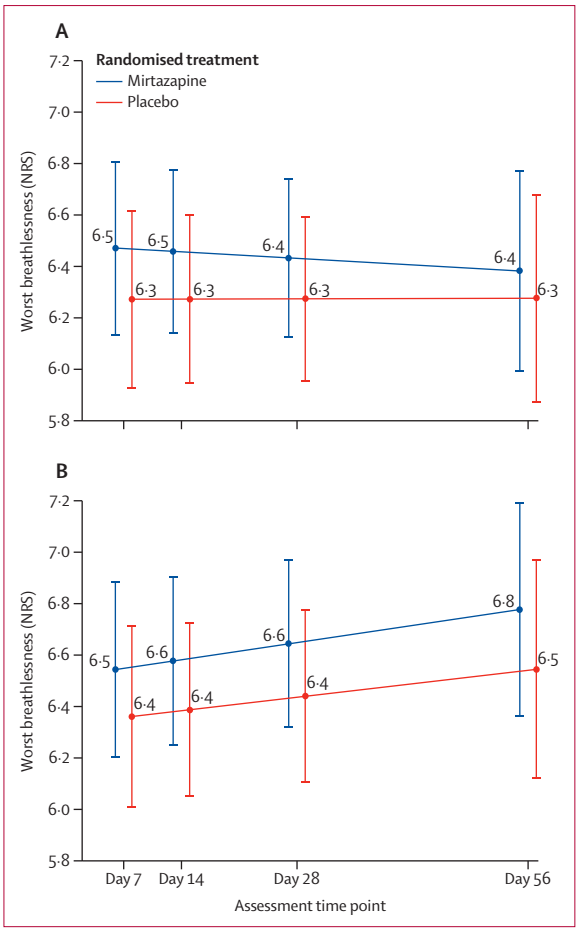

Figure 2: **Adjusted mean worst breathlessness (NRS) scores over the past 24 h, by timepoint and treatment arm, for the primary analysis (A) and the sensitivity analysis (B)**
Data are for the modified intention-to-treat population. NRS=numerical rating scale.

assessed by the hospital anxiety and depression scale, number and duration of episodes of breathlessness, Australia-modified Karnofsky performance scale, and generalised self-efficacy scale (appendix pp 19–33).

Pre-planned exploratory analyses, under both missing at random and missing not at random assumptions, found no evidence of a differential treatment effect by either disease type (COPD or interstitial lung diseases) or by hospital anxiety and depression scale anxiety or depression scores (appendix pp 39–40). The effect of anxiety or depression at baseline was also adjusted for in the primary endpoint analysis.

215 adverse reactions were reported in 72 (64%) of 113 participants receiving mirtazapine and 116 adverse reactions in 44 (40%) of 110 participants receiving placebo (table 3). 11 serious adverse events were reported in six (5%) of 113 participants receiving mirtazapine and eight serious adverse events were reported in seven (6%) of 110 participants receiving placebo; four participants (two [2%] of 113 receiving mirtazapine and two [2%] of 110 receiving placebo) had serious adverse events resulting in death before day 56. One (1%) participant receiving mirtazapine had a suspected unexpected serious adverse reaction.

Each category of hospital and informal carer data were skewed with a mode response of zero (appendix p 39). For each category, use was higher in the mirtazapine group than the placebo group (table 4). This finding persisted in treatment effect estimates, though no relationship was statistically significant.

31 qualitative interviews were performed in the two participating centres, 23 with participants (11 in the mirtazapine group, 12 in the placebo group) and eight with caregivers. In both study groups, most interviewees reported little change in participants' breathlessness or wellbeing. Some described fluctuations in their condition and noted that their symptoms went up and down without a clear pattern of improvement. Many participants expressed that they did not notice any changes in their health, including sleep, appetite, mood, and drowsiness. In both arms, a few participants expressed scepticism about the effectiveness of the trial medication and questioned whether they had received placebo or mirtazapine. Two participants shared favourable outcomes of the trial medication on their "chest". They said that the medication had alleviated their chest-related symptoms, particularly in the morning. Some participants reported side-effects including altered mental state, dizziness, memory and attention loss, dry mouth, increased urination, and mild diarrhoea. Despite these, in the qualitative analysis some participants expressed a readiness to restart treatment if efficacy was demonstrated.

Discussion

Chronic respiratory diseases like COPD and interstitial lung diseases present major clinical challenges due to their resulting breathlessness. This has substantial implications for quality of life, primary and secondary clinical care, and resource use, highlighting the need for innovative management strategies. Mirtazapine was tested based on its potential to modulate respiratory function, chemosensitivity, and anxiety, and its economic viability.[15] This study, which is to our knowledge the largest study to date on severe breathlessness in respiratory disease, found no significant difference between mirtazapine and placebo in alleviating breathlessness by day 56, and this was supported by secondary outcomes and sensitivity analysis accounting for missing data. Additionally, health and informal care use was higher in the mirtazapine group than the placebo group, possibly reflecting increased adverse or other events reported by that group.

Although mirtazapine showed promise in case series and feasibility studies, the absence of robust phase 3 trials before our study might have meant that the therapeutic

effect was overestimated. There are well recognised emotional and psychological mechanisms in the perception of breathlessness, and open-label, non-controlled clinical studies or case reports might report benefit simply because of the placebo effect, combined with regression to the mean, rather than being caused by the intervention tested. Our findings, coupled with the trial conducted by Currow and colleagues, which found no benefit from 25 to 100 mg of sertraline in 223 participants with breathlessness (mMRC scale ≥2)[16] and those from the small protriptyline trial,[33] imply that these antidepressants do not offer a viable therapeutic approach for alleviating breathlessness. Our population was focussed on people with respiratory disease, but the findings are likely relevant to individuals with breathlessness due to cancer, heart disease, and long COVID, due to some shared mechanisms of breathlessness perception.[13,15]

Our findings revealing the lack of benefit from mirtazapine alongside slightly higher adverse events and increased care use than with placebo underscore the importance of clinical trials in this population. Clinicians often feel compelled to act, assuming adverse events stem from disease progression. Off-label medicine usage is common in palliative care and advanced illness, constituting about a third of all prescriptions.[34] This practice is particularly pronounced in cases of breathlessness.[35] There is some evidence of off-label use of antidepressants for breathlessness. Our 2019 European survey found that 19% of respiratory physicians and 11% of palliative physicians would recommend an antidepressant "always or often" for severe breathlessness in COPD; the figures were 12% of respiratory physicians and 13% of palliative physicians for interstitial lung diseases.[9] Mirtazapine prescriptions have increased across various health-care settings, including UK primary care[36] and Australian aged care facilities, where usage rose from 8% to 21% of residents between 2006 and 2019.[37] Generic mirtazapine is readily available, raising concerns that the growing interest and case studies could result in broader off-label adoption, akin to benzodiazepines, without adequate evidence.

Clinical chart reviews indicate considerable variability in the prescription of off-label therapy in palliative care, ranging from 0% to 88% of prescriptions.[38] Upholding the ethical principle "do no harm" is paramount across all medical disciplines, including respiratory medicine and palliative care. For instance, Hui and colleagues tested the efficacy of high-dose dexamethasone in alleviating breathlessness in patients with cancer. Their study revealed that dexamethasone did not statistically significantly reduce breathlessness compared with placebo and was associated with more adverse events. They concluded that despite dexamethasone's widespread consideration among clinicians (up to 98% report considering it), dexamethasone cannot be routinely recommended to alleviate cancer-related breathlessness.[39]

	Mirtazapine (n=113)	Placebo (n=110)	Total (n=223)
Number of adverse reactions	215	116	331
Number of participants with one or more adverse reactions	72 (64%)	44 (40%)	116 (52%)
Number of adverse reactions per participant*			
0	41 (36%)	66 (60%)	107 (48%)
1	19 (17%)	17 (15%)	36 (16%)
2	20 (18%)	15 (14%)	35 (16%)
3	13 (12%)	5 (5%)	18 (8%)
4	8 (7%)	4 (4%)	12 (5%)
5	5 (4%)	0	5 (2%)
6	2 (2%)	0	2 (1%)
7	1 (1%)	0	1 (<1%)
8	2 (2%)	2 (2%)	4 (2%)
10	1 (1%)	0	1 (<1%)
15	1 (1%)	0	1 (<1%)
22	0	1 (1%)	1 (<1%)
Number of serious adverse events	11	8	19
Number of participants with one or more serious adverse event	6 (5%)	7 (6%)	13 (6%)
Number of SUSARs	1	0	1
Number of participants with one or more SUSAR	1 (<1%)	..	1 (<1%)
Number of serious adverse events per participant			
0	107 (95%)	103 (94%)	210 (94%)
1	2 (2%)	6 (6%)	8 (4%)
2	3 (3%)	1 (1%)	4 (2%)
3	1 (1%)	0	1 (<1%)
Serious adverse event MedDRA term†			
Cardiac disorders	1/11 (9%)	2/8 (25%)	3/19 (16%)
General disorders and administration site conditions	1/11 (9%)	0	1/19 (5%)
Infections and infestations	3/11 (27%)	2/8 (25%)	5/19 (26%)
Injury, poisoning and procedural complications	1/11 (9%)	1/8 (13%)	2/19 (11%)
Metabolism and nutrition disorders	1/11 (9%)	0	1/19 (5%)
Musculoskeletal and connective tissue disorders	1/11 (9%)	0	1/19 (5%)
Respiratory, thoracic, and mediastinal disorders	3/11 (27%)	1/8 (13%)	4/19 (21%)
Gastrointestinal disorders	0	2/8 (25%)	2/19 (11%)

SUSAR=suspected unexpected serious adverse reaction. *Most common adverse events occurring in the mirtazapine group were dry mouth, somnolence, fatigue, and sedation. †There was no poisoning, and infections included COVID infection.

Table 3: **Safety and toxicity**

	Outcome data: mean (SD)			Treatment effect: mirtazapine *vs* placebo (95% CI)
	Mirtazapine	Placebo	Total	
Acute hospital nights	0·99 (4·39)	0·48 (2·07)	0·74 (3·45)	0·57 (–0·48 to 1·62)
Emergency department admissions	0·10 (0·33)	0·07 (0·36)	0·09 (0·35)	0·02 (–0·07 to 0·12)
Outpatient visits	1·66 (2·63)	1·32 (1·98)	1·49 (2·33)	0·38 (–0·25 to 1·02)
Hours of family care	72·90 (153·29)	58·46 (142·72)	65·71 (148·29)	14·99 (–24·81 to 54·79)

Table 4: **Health-care use at the primary endpoint (day 56)**

A major strength of this pragmatic trial is its generalisability due to its ability to recruit the target population; individuals whose lives were restricted by severe breathlessness and co-morbidities across multiple centres and seven diverse countries. Participants had multiple symptoms, concerns, and often anxiety and depression, as exhibited on our palliative outcome, and respiratory measures.[4,16,23] We found consistent results across a variety of outcomes, including breathlessness, quality of life, safety, and care use. Qualitative insights from patient and caregiver interviews highlighted the persistent nature of breathlessness. These firsthand accounts emphasise the importance of patient-centred care in respiratory medicine.

To underpin future therapeutic strategies, alongside treatments targeting primary disease processes, it is important to improve therapies to alleviate severe breathlessness. There are three potential therapeutic approaches: lung-brain axis, which involves modifying respiratory sensation in the brain, as with opioids or, as we had hypothesised, mirtazapine; behavioural-functional axis, which focuses on reversing the cycle of disability through interventions like pulmonary rehabilitation; and psycho-social axis, which addresses social factors and emotional responses that exacerbate breathlessness, such as reducing panic. Given the complexity of breathlessness, effective clinical management will likely need to integrate all three approaches.

The limitations of this study included that many people were not eligible for the trial as they were already receiving antidepressants (n=482/1919, 25%) or because of other factors such as not having breathlessness at mMRC grade 3 or 4 or presence of cardiovascular disease or acute cardiac events within 3 months before randomisation. In addition, the heterogeneous nature of respiratory diseases, combined with individual variability in response to interventions, might have influenced the outcomes. We observed that optimal treatment varied across countries, for example access to pulmonary rehabilitation and other non-pharmacological treatments, such as breathlessness support services. The challenges posed by the COVID-19 pandemic and Brexit disruptions hampered recruitment and might have influenced the study's power to detect a statistically significant difference. Caution is needed when interpreting the exploratory subgroup analysis, due to the small numbers of participants in that analysis. Nonetheless, our results, including point estimates and corresponding 95% CIs, found that the pre-specified treatment effect, which the study was powered to detect, was not observed. This held true for both primary and sensitivity analyses, and analysis of secondary endpoints. Despite falling short of the recruitment target of 324 participants, the trial's outcome suggests, with 95% confidence, the absence of a clinical benefit from mirtazapine among the 225 participants enrolled. Continuing recruitment to reach the original planned 324 participants is unlikely to alter this conclusion. Furthermore, we found some differences in formal and informal care use. Full economic evaluation of mirtazapine versus placebo is warranted, considering aggregate resource use across formal and informal care as well as broad quality-of-life measures. This would aid in understanding whether the observed increased resource use associated with mirtazapine persists in a comprehensive economic analysis, which could have broader implications for off-label use of medications.

In conclusion, our trial did not show benefits of mirtazapine in this population and suggest it might slightly increase adverse events and care use. Based on existing best evidence, early identification and non-pharmacological approaches should be first-line treatment for the symptoms of breathlessness. These include an appropriately personalised approach to symptom management, with a continuum of approaches including pulmonary rehabilitation in earlier stages, interventions to improve peripheral muscle strength, and, when patients have more advanced disease, breathlessness support services that combine respiratory and palliative approaches, as all have been shown to be effective in randomised controlled trials and systematic reviews and are suggested in leading guidance such as by GOLD.[5] We observed that access to such interventions varies across and within countries. Future research endeavours should continue to rigorously develop and trial innovative therapeutic approaches, leveraging both pharmacological and non-pharmacological interventions, to address the multifaceted challenges posed by breathlessness in respiratory diseases. Our trial has identified ways such research can be achieved.

Contributors

Conceptualisation: IJH, STS, CB, MM, MK, JMBr, MC, CN, CJJ, AW. Methodology: IJH, MM, SB, KR, MC, MK, STS, CB, DCC, JMBr, STBr, PM, CN, MJJ, BF, AW. Validation: IJH, STBr, AOO, PM, MM, CN, MC, SB, JMBr, LG, BF. Formal analysis: IJH, STBr, JMBr, CN, PM, AOO, LG, MM, ET, HM, MC. Investigation: IJH, SB, KR, CB, STS, MJJ, SPH, CB, PJ, AOO, LG, AW. Funding acquisition: IJH, SB, JMBr, KR, CB, STS, MJJ, SPH, CB, ST, DCC, GM, CN. Data curation: IJH, STBr, JMBr, AOO, SB, HM, GM, PM. Verified the data: STBr, PM, CN, HM, AOO, LG, IJH. Writing: original draft: IJH. Writing (core elements): IJH, STBr, JMBr, AOO, PM. Writing (review, critical input & editing): IJH, STBr, AOO, PM, MM, CN, MC, SB, CB, STS, KR, DCC, MJJ, SPH, CJJ, HM, MK, ST, LG, CEB, ET, PJ, JMBr, GM, AW. Visualisation: STBr, HM, AOO, PM, IJH. Supervision: IJH, STBr, MM, CN, AOO, PM, JMBr, CB, STS, KR, GM. Project administration: IJH, AOO, MM, CN, MC, GM. Funding acquisition: IJH, MM, SB, KR, MC, MK, STS, CB, DCC, MJJ, JMBr, STBr, CJJ, AW. All authors critically reviewed the manuscript and approved the final version. All authors were permitted to access all the data, and all authors accept responsibility to submit the manuscript for publication.

Declaration of interests

IJH reports grants from EU, Marie Curie Cancer Care, and National Institute for Health and Care Research (NIHR), and is Scientific Director of Cicely Saunders International, NIHR Emeritus Senior Investigator, and is an Honorary Clinical Consultant in Palliative Medicine for hospitals under Kings College Hospital National Health Service Foundation Trust outside of the submitted work. CEB reports grants from the EU, NIHR, AstraZeneca as well as an industry collaboration and a personal fee from Roche outside of the submitted work.

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Data sharing

Data collected for the study, including de-identified participant data, data dictionary, and additional related documents, will be made available to others upon request to better-b@kcl.ac.uk, according to the King's College London data sharing policy and in accordance with WHO statement on public disclosure of clinical trial results.

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