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BETTER-B: Better Treatments for Refractory Breathlessness

Submission date	Recruitment status	[X] Prospectively registered
11/11/2019	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
19/11/2019	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
18/08/2025	Respiratory	

Plain English summary of protocol

Current plain English summary as of 29/09/2020:
Background and study aims
Breathlessness which affects people with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) even when they are receiving treatment is called refractory breathlessness. It can be frightening and cause: distress, disability, anxiety and social isolation. We don't know which treatment is best for refractory breathlessness and this study aims to test whether a widely used drug called Mirtazapine can help to reduce the symptoms of refractory breathlessness when compared to a dummy drug or 'placebo'.

Caregiver part of the study
We are also finding out how refractory breathlessness affects caregivers such as close family members. Through questionnaires, we are collecting information about the caregiver's views of the refractory breathlessness that is affecting the person that they are caring for and how providing care affects the caregiver.

Who can participate?
Patients who are at least 18 years old, have COPD and/or ILD, and have severe breathlessness as assessed by your doctor

What does the study involve?
Main Study
The study team want to recruit 324 participants from 5 countries. The participants taking part are put into 1 of 2 groups at random. Neither you nor your doctor will be able to decide or know which group you are in.
One group will receive the drug mirtazapine which is being tested as a treatment and the other group will receive a dummy drug called the placebo. The drugs will be given as tablets which will be swallowed as one tablet per day for 56 days. Several study visits will take place, some will be face to face at hospital and some will be over the telephone. If your breathlessness does not get better after 14 days, you can take two tablets per day. If your breathlessness still does not get better after 28 days, you can take up to three tablets per day. During your study visits, you will also be asked to complete questionnaires about your personal experience of breathlessness and how it affects your quality of life.

Caregiver part of the study
Caregivers taking part in the caregiver part of the study will be asked to complete quality of life questionnaire booklets about their view of how breathlessness is affecting the person that they are caring for and how giving care affects themselves. This study will take place over several meetings, some will be face to face and some will be over the telephone.

What are the possible benefits and risks of participating?
We do not know the best way to treat refractory breathlessness and it is hoped that by taking part in this study you will help to find out whether Mirtazapine is an effective treatment and whether it helps to improve quality of life for those with COPD or ILD.
Taking part will involve commitment of your time to attend hospital visits or join in phone calls with the study team and to complete the forms and questionnaires. The mirtazapine treatment used as part of the study is widely used in the treatment of depression and it has fewer unwanted side effects when compared to other drugs used for the same purpose. It does still have side effects, the most common include:
reduced anxiety, increased appetite, reduced nausea, pain relief, weight gain, drowsiness, dizziness, fatigue, and dry mouth

Where is the study run from?
The study is being run by Co-Sponsors King's College London and University College Dublin in collaboration with Leeds Clinical Trials Research Unit (CTRU). The total recruitment target is 324. There are 12 sites in total with three UK partners taking part, University of Nottingham, Hull York Medical School, and King's College London, with the latter being the lead site. Internationally, we have 9 sites running in Ireland, Italy, Germany and Poland.

When is the study starting and how long is it expected to run for?
January 2019 to June 2023

Who is funding the study?
The study is funded by the EU through the Horizon 2020 programme.

Who is the main contact?
Irene Higginson (Scientific)
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Emma Batman
Clinical Trial Co-ordinator
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Better-b@kcl.ac.uk

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Previous plain English summary as of 15/04/2020:

Background and study aims
Breathlessness which affects people with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) even when they are receiving treatment is called refractory breathlessness. It can be frightening and cause: distress, disability, anxiety and social isolation.

We don't know which treatment is best for refractory breathlessness and this study aims to test whether a widely used drug called Mirtazapine can help to reduce the symptoms of refractory breathlessness when compared to a dummy drug or 'placebo'.

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Main Study
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Where is the study run from?
The study is being run by Co-Sponsors King's College London and University College Dublin in collaboration with Leeds Clinical Trials Research Unit (CTRU). The total recruitment target is 324. There are 11 sites in total with three UK partners taking part, University of Nottingham, Hull York Medical School and King's College London, with the latter being the lead site. Internationally, we have 8 sites running in Ireland, Italy, Germany and Poland.

When is the study starting and how long is it expected to run for?
The study will aim to begin recruitment in September 2020 for 18 months until March 2022

Who is funding the study?
The study is funded by the EU through the Horizon 2020 programme.

Who is the main contact?
Claire Dimbleby
Senior Trial Manager
ctru-betterb@leeds.ac.uk

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Previous plain English summary:

Background and study aims
Breathlessness which affects people with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) even when they are receiving treatment is called refractory breathlessness. It can be frightening and cause: Distress, disability, anxiety, social isolation.
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When is the study starting and how long is it expected to run for?
The study will aim to begin recruitment in March 2020 for 24 months until March 2022

Who is funding the study?
The study is funded by the EU through the Horizon 2020 programme.

Who is the main contact?
Claire Dimbleby
Senior Trial Manager
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Contact information

Type(s)
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Additional identifiers

Clinical Trials Information System (CTIS)
2019-002001-21

Integrated Research Application System (IRAS)
264831

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Version 8.0; IRAS 264831

Study information

Scientific Title
An international, multicentre, randomised controlled pragmatic trial of mirtazapine to alleviate breathlessness in palliative and end of life care

Acronym
BETTER-B

Study objectives
The aim of the study is to assess the effectiveness and cost-effectiveness of mirtazapine for the reduction of patient-reported chronic or refractory breathlessness and quality of life in patients with COPD or ILD and at end of life, and on the caregiver burden and experience of their caregivers and close family members.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/05/2020, London Bridge Research Ethics Committee (Skipton House, 80 London Road, London, SE1 6LH, UK; londonbridge.rec@hra.nhs.uk), REC ref: 20/LO/0369

Study design
International multicentre phase III double-blind randomized placebo-controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Refractory breathlessness in patients with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD), including chronic fibrotic lung disease following SARS-CoV-2 infection

Interventions
Current interventions as of 15/04/2020:

Participants with refractory breathlessness and COPD/ILD will be randomised on a 1:1 basis to receive either oral Mirtazapine (starting dose 15 mg per day) or placebo (one tablet per day), using minimisation incorporating a random element. Minimisation factors used will be: disease (COPD, ILD); HADS anxiety and depression subscale scores; receipt of opioids and recruiting site.

Participants will be eligible for dose escalation to 30 mg per day at Day 14 (or two tablets of placebo) and to 45 mg per day at Day 28 (or three tablets of placebo) of the treatment period. Treatment will continue until day 56.

Participant follow-up assessments will take place at days 7, 14, 28 and 56 post start of treatment. Participants will be followed up 7 days after completing trial treatment (including dose tapering) to assess safety and toxicity of treatment.

At the end of the day 56 post start of treatment, and after dose tapering, if the participant wishes to take mirtazapine off trial, they should discuss this further with their GP.

Once the trial is open label, participants may request off trial mirtazapine from their family doctor/clinical team if they wish to do so irrespective of study arm (and maintaining blinding).

Participants will be followed-up at 180 days post start of treatment via phone to complete the final participant reported questionnaires.

Participants will be randomised using a central automated 24-hour telephone/internet service based at the Leeds CTRU.

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Previous interventions:

Participants with refractory breathlessness and COPD/ILD will be randomised on a 1:1 basis to receive either oral Mirtazapine (starting dose 15 mg per day) or placebo (one tablet per day), using minimisation incorporating a random element. Minimisation factors used will be: disease (COPD, ILD); HADS anxiety and depression subscale scores; receipt of opioids and recruiting site.

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Participant follow-up assessments will take place at days 7, 14, 28 and 56 post start of treatment. Participants will be followed up 7 days after completing trial treatment (including dose tapering) to assess safety and toxicity of treatment.

At the end of the day 56 post start of treatment, and after dose tapering, the trial becomes open label.

Once the trial is open label, participants may request off trial mirtazapine from their family doctor/clinical team if they wish to do so irrespective of study arm (and maintaining blinding).

Participants will be followed-up at 180 days post start of treatment via phone to complete the final participant reported questionnaires.

Participants will be randomised using a central automated 24-hour telephone/internet service based at the Leeds CTRU.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Oral Mirtazapine

Primary outcome(s)
Self-reported worst breathlessness over the past 24 hours measured at day 56 post start of treatment using a numerical rating scale (NRS, 0=no breathlessness to 10=worst possible breathlessness)

Key secondary outcome(s))
Current secondary outcome measures as of 15/04/2020:

1. Worst breathlessness over the last 24 hours as assessed by NRS (0=no breathlessness to 10=worst possible breathlessness) at days 7, 14, 28 and 180 post start of treatment
2. Average breathlessness over the last 24 hours assessed by NRS (0=no breathlessness to 10=worst possible breathlessness) at days 7, 14, 28, 56 and 180 post start of treatment
3. Number and duration of episodes of breathlessness over the last 24 hours
4. Physical and emotional aspects of breathlessness (Dyspnoea, fatigue, emotional function, mastery) as assessed by the Chronic Respiratory Questionnaire (CRQ) at days 14, 28, 56 and 180 post start of treatment
5. Physical symptoms as assessed by the Integrated Palliative care Outcome Scale (IPOS) at days 14, 28, 56 and 180 post start of treatment
6. Quality of Life (QoL) as assessed by the EQ-5D-5L and associated VAS at days 14, 28, 56, 180 post start of treatment and Australia-modified Karnofsky Performance Scale (AKPS) at days 14, 28, 56 and 180 post start of treatment
7. Anxiety and depression as assessed by the Hospital Anxiety and Depression Scale (HADS) at days 28, 56, and 180 post start of treatment
8. Perceived self-efficacy as measured by the Generalized Self-Efficacy Scale (GSES) at day 56 post start of treatment
9. The consumption of opioids as measured by opioid medication usage at days 7, 14, 28, 56 and 180 post start of treatment
10. Healthcare services received, including out of hours care, number of emergency hospital attendances and admissions within 28 and 56 days post start of treatment and in the 3 month period prior to day 180 post start of treatment as measured by the Client Services Receipt Inventory (CSRI)
11. Safety as assessed by the occurrence of:
11.1. SAEs, SARs and SUSARs coded according to mild, moderate, or severe as reported at days 7, 14, 28 and 56 post start of treatment
11.2. Deaths by day 56 and day 180 post start of treatment
12. Toxicity as assessed by adverse reactions (ARs) coded according to mild, moderate, or severe as reported at days 7, 14, 28 and 56 post start of treatment
13. Tolerability as assessed by the proportion of patients not withdrawing due to adverse reactions
14. Baseline demographics and characteristics will be measured to enable prognostic evaluation of those factors most associated with benefit from mirtazapine (benefit as measured by worst breathlessness over the last 24 hours at day 56 post start of treatment. Specifically assessing:
14.1. Age
14.2. Gender
14.3. Functional status (as measured by actual functioning using AKPS, mobility using EQ-5D-5L, and ‘poor mobility’ using IPOS), aetiology (COPD /ILD)
14.4. Baseline intensity of breathlessness (as measured by worst breathlessness over the last 24 hours at baseline)
14.5. Anxiety and depression (as measured by HADS)
14.6. Concomitant opioid administration
15. Formal and informal care use over the previous period as measured by the Client Services Receipt Inventory (CSRI) at days 28, 56, and 180 post start of treatment, to examine hours of care and (using country specific unit costs) costs of services
16. Acceptability of the offered treatment as assessed by the recruitment conversion rate, the number of people withdrawing from treatment, and the number of participants who request mirtazapine from their doctor/clinician after 56 days post start of treatment
17. Treatment compliance as measured by the:
17.1. Proportion and type of dropouts over 56 days post start of treatment
17.2. Proportion of tablets taken over 56 days post start of treatment

17.3. Proportion of participants who escalate dose at days 14 and 28 post start of treatment
17.4. Off trial treatment compliance to 180 days post start of treatment
18. Caregiver's perceived impact on the participant and themselves as measured by:
18.1. Worst and average rating of the participant's breathlessness over the last 24 hours as assessed by NRS (0=no breathlessness to 10=worst possible breathlessness) at days 28, 56, and 180 post start of treatment;
18.2. Caregiver assessment of the participant's number and duration of episodes of breathlessness over the last 24 hours;
18.3. Informal care hours as measured by the Client Services Receipt Inventory (CSRI) at days 28, 56, and 180 post start of treatment;
18.4. Caregiver self-reported burden as measured by the Zarit Burden inventory at days 28, 56, and 180 post start of treatment;
18.5. Caregiver self-reported experiences of caregiving as measured by the Positive Aspects of Caregiving Scale (PAC) at days 28, 56, and 180 post start of treatment;
18.6. Caregiver perspectives on participants' situation as measured by the Integrated Palliative care outcome scale (IPOS) at days 28, 56, and 180 post start of treatment.
18.7. Caregiver overall health and wellbeing as measured by EQ-5D-5L and associated VAS at days 28, 56, and 180 post start of treatment

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Previous secondary outcome measures:

1. Worst breathlessness over the last 24 hours as assessed by NRS (0=no breathlessness to 10=worst possible breathlessness) at days 7, 14, 28 and 180 post start of treatment
2. Average breathlessness over the last 24 hours assessed by NRS (0=no breathlessness to 10=worst possible breathlessness) at days 7, 14, 28, 56 and 180 post start of treatment
3. Number and duration of episodes of breathlessness over the last 24 hours
4. Physical and emotional aspects of breathlessness (Dyspnoea, fatigue, emotional function, mastery) as assessed by the Chronic Respiratory Questionnaire (CRQ) at days 14, 28, 56 and 180 post start of treatment
5. Physical symptoms as assessed by the Integrated Palliative care Outcome Scale (IPOS) at days 14, 28, 56 and 180 post start of treatment
6. Quality of Life (QoL) as assessed by the EQ-5D-5L and associated VAS at days 14, 28, 56, 180 post start of treatment and Australia-modified Karnofsky Performance Scale (AKPS) at days 14, 28, 56 and 180 post start of treatment
7. Anxiety and depression as assessed by the Hospital Anxiety and Depression Scale (HADS) at days 28 and 56 post start of treatment
8. Perceived self-efficacy as measured by the Generalized Self-Efficacy Scale (GSES) at day 56 post start of treatment
9. The consumption of opioids as measured by opioid medication usage at days 7, 14, 28, 56 and 180 post start of treatment
10. Healthcare services received, including out of hours care, number of emergency hospital attendances and admissions within 28, 56 and 180 days post start of treatment
11. Safety as assessed by the occurrence of:
11.1. SAEs, SARs and SUSARs coded according to the Common Terminology Criteria for Adverse Events (CTCAE) categorisation (v5) as reported at days 7, 14, 28 and 56 post start of treatment
11.2. Deaths by day 56 and day 180 post start of treatment
12. Toxicity as assessed by adverse reactions (ARs) coded according to the Common Terminology Criteria for Adverse Events (CTCAE) categorisation (v5) as reported at days 7, 14, 28 and 56 post start of treatment
13. Tolerability as assessed by the proportion of patients not withdrawing due to adverse

reactions
14. Baseline demographics and characteristics will be measured to enable prognostic evaluation of those factors most associated with benefit from mirtazapine (benefit as measured by worst breathlessness over the last 24 hours at day 56 post start of treatment. Specifically assessing:
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14.5. Anxiety and depression (as measured by HADS)
14.6. Concomitant opioid administration
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17. Treatment compliance as measured by the:
17.1. Proportion and type of dropouts over 56 days post start of treatment
17.2. Proportion of tablets taken over 56 days post start of treatment
17.3. Proportion of participants who escalate dose at days 14 and 28 post start of treatment
17.4. Open label treatment compliance to 180 days post start of treatment
18. Caregiver's perceived impact on the participant as measured by:
18.1. Worst and average rating of the participant's breathlessness over the last 24 hours as assessed by NRS (0=no breathlessness to 10=worst possible breathlessness) at days 28, 56 and 180 post start of treatment;
18.2. Caregiver assessment of the participant's number and duration of episodes of breathlessness over the last 24 hours;
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18.6. Caregiver perspectives on participants' situation as measured by the Integrated Palliative care outcome scale (IPOS) at days 28, 56 and 180 post start of treatment.
18.7. Caregiver overall health and wellbeing as measured by EQ-5D-5L and associated VAS at days 28, 56 and 180 post start of treatment

Completion date
30/06/2023

Eligibility

Key inclusion criteria
Current inclusion criteria as of 29/09/2020:

1. Aged≥ 18 years old
2. Diagnosed with:
2.1. Chronic obstructive pulmonary disease (COPD), and/or

2.2. Interstitial lung disease (ILD), including chronic fibrotic lung disease following SARS-CoV-2 infection
3. Breathlessness severity: Modified MRC breathlessness scale of:
3.1. Grade 3 (I stop for breath after walking about 100 yards or after a few minutes on level ground) or
3.2. Grade 4 (I am too breathless to leave the house or I am breathless when dressing or undressing)
4. On optimal treatment of the underlying condition in the opinion of the identifying clinician (see section 0 of protocol for guidance)
5. Management of the underlying condition unchanged for the previous 2 weeks
6. Reversible causes of breathlessness optimally treated in the opinion of the identifying clinician
7. If female, must be (as documented in patient notes):
7.1. Postmenopausal (no menses for 12 months without an alternative medical cause), or
7.2. Surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy), or
7.3. Using acceptable contraception (which must be continued for 7 days after the last dose of IMP)
8. Able to complete questionnaires and trial assessments
9. Able to provide written informed consent

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Previous inclusion criteria:

1. Aged ≥18 years old
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8. Able to complete questionnaires and trial assessments
9. Able to provide written informed consent

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group

Adult

Lower age limit
18 years

Sex
Not Specified

Key exclusion criteria
Current exclusion criteria as of 29/09/2020:

1. Existing antidepressant use , or other serotonergic active substances (e.g. linezolid, St John's wort)
2. Known contraindication to mirtazapine
3. Hypersensitivity to the active substance or to any of the components of mirtazapine or placebo (e.g. lactose intolerance)
4. Australia modified Karnofsky Performance Scale ≤40
5. Pregnant or breast-feeding women. For women of childbearing potential (those not post-menopausal or surgically sterile) this must be confirmed by a pregnancy test (urine) within 7 days prior to randomisation
6. Patients with acute cardiac events within 3 months prior to randomisation (e.g. myocardial infarction, unstable angina pectoris, or significant cardiac conduction disturbance) in the opinion of the identifying clinician
7. Patients with jaundice or known hepatic impairment in the opinion of the identifying clinician (e.g. bilirubin >25micromol/L, and AST and ALT >2 times upper limit of normal)
8. Patients with known renal impairment in the opinion of the identifying clinician (e.g. creatinine >132micromol/L and eGFR <30mL/min/1.73m2)
9. Uncontrolled blood pressure in the opinion of the identifying clinician
10. Uncontrolled diabetes mellitus in the opinion of the identifying clinician
11. Uncontrolled seizures, epilepsy or organic brain syndrome in the opinion of the identifying clinician
12. Severe depression or suicidal thoughts in the opinion of the identifying clinician
13. History of psychotic illness (schizophrenia, or other psychotic disturbances) in the opinion of the identifying clinician
14. Bipolar disorder, or a history of mania or hypomania in the opinion of the identifying clinician
15. Currently enrolled in another interventional trial
16. Patients with known congenital QT prolongation or family history for QT prolongation
17. Use of medicines that cause QT prolongation such as macrolides and typical antipsychotics (unless required in low-dose to relieve nausea, e.g. haloperidol ≤5mg/24h, levomepromazine ≤25mg/24h)
18. Patients with a known history of suicide-related events

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10. Uncontrolled diabetes mellitus in the opinion of the identifying clinician
11. Uncontrolled seizures, epilepsy or organic brain syndrome in the opinion of the identifying clinician
12. Severe depression or suicidal thoughts in the opinion of the identifying clinician
13. History of psychotic illness (schizophrenia, or other psychotic disturbances) in the opinion of the identifying clinician
14. Bipolar disorder, or a history of mania or hypomania in the opinion of the identifying clinician
15. Currently enrolled in another interventional trial

Date of first enrolment
01/02/2021

Date of final enrolment
31/12/2022

Locations

Countries of recruitment
United Kingdom

England

Germany

Ireland

Italy

Poland

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Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Organisation
University College Dublin

ROR
https://ror.org/05m7pjf47

Funder(s)

Funder type
Government

Funder Name
European Union Horizon 2020 Research and Innovation Programme (Grant No. 825319)

Results and Publications

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		06/09/2024	16/09/2024	Yes	No
Results article		14/08/2025	18/08/2025	Yes	No
HRA research summary			28/06/2023	No	No

Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes