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BETTER-B (Aus): Better treatments for refractory breathlessness

Submission date 18/05/2020	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 09/06/2020	**Overall study status** Completed	
Last Edited 16/09/2024	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims
Chronic obstructive pulmonary disease (COPD) is the name for a group of lung conditions that cause breathing difficulties. Interstitial (in-tur-STISH-ul) lung disease (ILD) describes a large group of disorders, most of which cause progressive scarring of lung tissue
Breathlessness which affects people with COPD and 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'.

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
We are also finding out how refractory breathlessness affects caregivers such as close family members. 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?
This is the Australian recruitment to a larger study being run by Co-Sponsors King's College London and University College Dublin. The total recruitment target is 324. The Australian recruitment of 50 people will involve sites in New South Wales, Victoria, and from Christchurch in New Zealand.

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 July 2024

Who is funding the study?
The Australian arm of this study is funded by the National Health and Medical Research Council.

Who is the main contact?
Prof. David Currow (scientific), dcurrow@uow.edu.au
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Study website
https://betterbreathe.eu/

Contact information

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
048/20 V1.0

Study information

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

Acronym
BETTER-B (AUS)

Study objectives
The aim of the trial is to assess the clinical and cost-effectiveness of mirtazapine for the reduction of patient-reported chronic or refractory breathlessness and quality of life in patients with chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD) in palliative and end of life care. The trial will also assess caregiver burden and the experience of caregivers and close family members.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 21/08/2020, Western Sydney Local Health District Human Research Ethics Committee (Research Office, Level 2, REN Building, Westmead Hospital, Hawkesbury & Darcy Roads, Westmead, NSW 2145, Australia; +61 (0)2 8890 9007; WSLHD-ResearchOffice@health.nsw.gov.au), ref: 2020/ETH01506

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

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Home, Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Refractory breathlessness in patients with a chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD)

Interventions
Participants will be randomised via minimisation in a 1:1 ratio to receive either oral mirtazapine or placebo medication for 56 days. Minimisation factors used will be: disease (COPD, ILD); HADS (Hospital Anxiety and Depression Scale); receipt of opioids and recruiting site.
Participants will be treated with 15 mg/day of oral mirtazapine or placebo equivalent with two assessments for dose escalation (at days 14 and 28 of treatment). At both assessments, patient-reported breathlessness intensity (“at worst” over the previous 24 hours) will be recorded using the numerical rating scale (NRS). If there is no improvement in NRS and the drug has been well-tolerated and adhered to, the daily dose of treatment will be increased: at day 14, by 15 mg/day to 30 mg/day (or placebo), at day 28, by 15 mg/day to 30 mg/day or 45 mg/day (or placebo). Participants 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, participants discontinue trial treatment. Following the end of treatment assessments at 7 days post end of treatment, 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.

Caregiver part of study:
There will be no separate randomisation process for caregivers as they will be identified by the same trial number as the randomised participant they are caregiver for. Where caregivers consent to take part, the caregiver will give their assessment of the participant and also complete the caregiver questionnaires at baseline, day 28, 56 and 180.

Qualitative sub-study:
Trial participants (including caregivers) may be invited to take part in a qualitative sub-study to explore barriers to uptake of the medicine and its implementation across different cultures, socio-economic and other groups, taking into account gender, religious, cultural and personal beliefs.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Mirtazepine

Primary outcome measure
Self-reported worst breathlessness over the last 24 hours at day 56 post start of treatment as assessed by numerical rating scale (NRS, 0=no breathlessness to 10=worst possible breathlessness)

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, 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

Overall study start date
31/07/2020

Completion date
31/12/2024

Eligibility

Key inclusion criteria
Patients:
1. Aged ≥18 years old
2. Diagnosed with:
2.1. Chronic obstructive pulmonary disease (COPD), and/or
2.2. Interstitial lung disease (ILD)
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 the section 9.3.3 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

Carers:
10. Identified by an included participant as the person closest to them
11. Aged ≥18 years
12. Able to complete questionnaires and assessments
13. Able to provide written informed consent

Participant type(s)
Patient, Carer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
50

Total final enrolment
20

Key exclusion criteria

Patients:
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. 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. 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. Known renal impairment in the opinion of the identifying clinician (e.g. creatinine >132micromol/L and eGFR <30mL/min/1.73m2 x)
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

Carers:
There are no specific exclusion criteria for caregivers.

Date of first enrolment
18/05/2021

Date of final enrolment
31/05/2024

Locations

Countries of recruitment
Australia

New Zealand

Study participating centre
Westmead Hospital
Cnr Hawkesbury Road and Darcy Road
Westmead NSW
Australia
2145

Study participating centre
Concord Hospital
Hospital Road
Concord
Australia
2139

Study participating centre
Calvary Health Care
91-111 Rocky Point Road
Kogarah
Australia
2217

Study participating centre
University Hospital Geelong
Bellerine St
Geelong
Australia
3220

Study participating centre
McKellar Centre
45-95 Ballarat Rd
North Geelong
Australia
3215

Study participating centre
Christchurch Hospital
2 Riccarton Avenue
Christchurch Central City
New Zealand
8011

Sponsor information

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Sponsor type
University/education

Website
https://www.uts.edu.au/itcc/itcc-team

ROR
https://ror.org/03f0f6041

Funder(s)

Funder type
Government

Funder Name
National Health and Medical Research Council

Alternative Name(s)
NHMRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Australia

Results and Publications

Publication and dissemination plan

Planned publication of study protocol and main trial analysis in an open access, high-impact, peer-reviewed journal.

Intention to publish date
30/06/2025

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be included in the subsequent results publication.

Added 10/01/2024:
The datasets generated during and/or analysed during the current study will be available upon request.
The name and email address of the investigator/body who should be contacted for access to the datasets: David Currow (dcurrow@uow.edu.au).
The type of data that will be shared: Individual Participant Data as csv files, de-identified.
Dates of availability: 5 years post publication of the main results.
Whether consent from participants was required and obtained: Specific participant consent for the sharing of their data for extended or unrelated use was not obtained.
Comments on data anonymization: All participant-level data is by unique PID only, with potentially identifiable information to be removed prior to sharing, such as postcode and date of birth (year and age only will be provided).
Any ethical or legal restrictions: Future researchers will be required to seek a waiver of consent from the approving Ethics Committee, and will be required to provide the proposed project details in order to access the IPD.
Any additional comments: This data will later be made available via the Health Data Australia catalogue.

IPD sharing plan summary
Available on request, Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		06/09/2024	16/09/2024	Yes	No