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Better treatments for refractory breathlessness

Submission date 31/05/2016	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 13/06/2016	**Overall study status** Completed	
Last Edited 15/12/2022	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims
Breathlessness is a common symptom affecting 50-70% of people with cancer and over 90% of people with non-cancer lung disease. In some cases, even when the underlying causes are treated, the breathlessness itself continues (refractory breathlessness). This can be very distressing, causing fear and panic; reduced quality of life, including social life; and can result in emergency hospital admissions. At the moment, there is no standard treatment for refractory breathlessness. This study is looking at a commonly used antidepressant drug called mirtazapine, which is used to treat depression and anxiety. This drug affects a brain chemical called serotonin, which is active when people are breathless. Reports involving small numbers of patients suggest that mirtazapine may be an effective treatment for breathlessness, possibly because it also reduces feelings of panic. The aim of this study is to find out whether conducting a small trial looking at the effectiveness of mirtazapine in the treatment of refractory breathlessness is feasible and whether enough patients can be recruited to take part.

Who can participate?
Adult patients with cancer or non-cancer lung disease experiencing refractory breathlessness.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group take 15mg tablets of mirtazapine every day for 28 days. Half way through the study (day 14) participants have their breathlessness assessed on a numbered scale to find out if it has improved. If there is no improvement and the drug is not causing any side effects, then the dose is doubled for the remaining 14 days of the study. Those in the second group take a placebo (dummy pill) every day for 28 days. Participants are then followed up for seven days following completion of the study to find out if their breathlessness has improved. After 12 months, the number or participants recruited to the study are recorded in order to find out if enough patients could be recruited.

What are the possible benefits and risks of participating?
Not provided at time of registration.

Where is the study run from?
1. Kings College Hospital (UK)
2. Castle Hill Hospital (UK)
3. Hull Royal Infirmary (UK)

4. Nottingham City Hospital Campus (UK)
5. Queens Medical Centre Campus (UK)

When is the study starting and how long is it expected to run for?
November 2015 to January 2018

Who is funding the study?
Marie Curie Cancer Care (UK)

Who is the main contact?
Dr Heather Cook
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2015-004064-11

Protocol serial number
30471

Study information

Scientific Title
BETter TreatmEnts for Refractory Breathlessness: A feasibility study of the use of mirtazapine for refractory breathlessness

Acronym
BETTER-B (Feasibility)

Study objectives
The aim of this study is to determine the feasibility of conducting a large-scale randomised, double-blind, placebo-controlled study of mirtazapine for refractory breathlessness.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - Central Research Ethics Committee, 29/01/2016, ref: 16/LO/0091

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Specialty: Respiratory disorders, Primary sub-specialty: Respiratory disorders; UKCRC code/ Disease: Respiratory/ Other diseases of the respiratory system

Interventions
Participants will be randomised via minimisation on a 1:1 ratio to receive either oral mirtazapine (15mg/day) or placebo medication for 28 days. At day 14 of treatment breathlessness intensity ("at worst" over the previous 24 hours) will be assessed using the numerical rating scale (NRS). If there is no improvement in NRS (i.e. NRS does not increase by 1 point or more compared to baseline NRS) and the drug has been well tolerated, the daily dose of treatment will be doubled.

Participants will be followed up by phone 7 days after the end of trial treatment to assess whether any adverse events or reactions have occurred.

Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome(s)
Recruitment rate is measured by the number of patients recruited across three hospitals over 12 months.

Key secondary outcome(s))
Feasibility:
1. Number of patients screened for eligibility and reasons for non-eligibility
2. Proportion of eligible patients randomised and reasons for non-randomisation
3. Proportion of patients for which blinding is maintained
4. Proportion of research assessors for which blinding is maintained
5. Proportion of patients remaining on study for 28 days
6. Proportion of and reasons for patients with missing data for trial outcomes

7. Proportion of patients who would be eligible for dose escalation at 28 days
8. Treatment compliance over the period

Activity, symptoms and quality of life:
1. Breathlessness mastery is assessed using the Chronic Respiratory Questionnaire (CRQ) and modified Medical Research Council (mMRC) dyspnoea scale on day 14 and day 28
2. Lower extremity functioning is measured using the Short Physical Performance Battery (SPPB) on day 28
3. Coping self-belief is measured using the Generalized Self-Efficacy Scale (GSES) on day 28
4. Palliative symptoms is measured using the Integrated Palliative care Outcome Scale (IPOS) on day 14 and day 28
5. Anxiety and depression are measured using the Hospital Anxiety and Depression Scale (HADS) on day 14 and day 28
6. Quality of life is measured using the EQ-5D-5L on day 28 and Australian-modified Karnofsky Performance Scale (AKPS) on day 14 and day 28
7. Health Economics are assessed using the Client Services Receipt Inventory (CSRI) on day 28

Safety and toxicity:
1. Adverse reactions are assessed using the Common Terminology Criteria for Adverse Events (CTCAE) categorisation on days 7, 14, 21 and 28
2. Occurrence of SAEs, SARs and SUSARs
3. Opioid medication is assessed on days 7, 14, 21 and 28

Completion date
26/12/2018

Eligibility

Key inclusion criteria
1. Male or female aged ≥ 18 years old
2. Modified MRC dyspnoea scale grade 3 or 4
3. Diagnosis of either:
3.1. Cancer
3.2. Chronic obstructive pulmonary disease (COPD)
3.3. Interstitial lung disease (ILD)
3.4. Chronic heart failure (New York Heart Association class III or IV)
4. On optimal treatment of the underlying condition in the opinion of the identifying clinician
5. Management of the underlying condition unchanged for the previous 1 week
6. Reversible causes of breathlessness optimally treated in the opinion of the identifying clinician
7. Expected prognosis of ≥2 months
8. If female and of child-bearing potential, must agree to use adequate contraception
9. Able to complete questionnaires and trial assessments
10. Able to provide written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group

Adult

Lower age limit
18 years

Sex
All

Total final enrolment
64

Key exclusion criteria
1. Existing antidepressant use
2. Known contraindication to mirtazapine
3. Hypersensitivity to the active substance or to any of the components of the mirtazapine or placebo (e.g. lactose intolerance)
4. Australia modified Karnofsky Performance Scale ≤40
5. Pregnant or breast-feeding women
6. Patients with acute cardiac events within 3 months of randomisation (myocardial infarction, unstable angina pectoris, or significant cardiac conduction disturbance)
7. Patients with known hepatic impairment
8. Patients with known renal impairment
9. Patients with uncontrolled blood pressure
10. Patients with uncontrolled diabetes mellitus
11. Patients with uncontrolled seizures, epilepsy or organic brain syndrome
12. Patients with severe depression or suicidal thoughts
13. Patients with a history of psychotic illness (schizophrenia, bipolar disorder, mania or hypomania, or other psychotic disturbances)

Date of first enrolment
01/08/2016

Date of final enrolment
31/07/2017

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Kings College Hospital
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Castle Hill Hospital
Castle Road
Cottingham
United Kingdom
HU16 5JQ

Study participating centre
Hull Royal Infirmary
Anlaby Road
Hull
United Kingdom
HU3 2JZ

Study participating centre
Nottingham City Hospital Campus
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Study participating centre
Queens Medical Centre Campus
Lister Road
Nottingham
United Kingdom
NG7 2RT

Sponsor information

Organisation
Kings College Hospital NHS Foundation Trust

ROR
https://ror.org/01n0k5m85

Funder(s)

Funder type
Charity

Funder Name
Marie Curie Cancer Care

Alternative Name(s)
Marie Curie Cancer Care, MarieCurieUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/02/2020	10/01/2020	Yes	No
Results article	qualitative results	22/02/2020	24/02/2020	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file	version 2.0	11/02/2016	15/12/2022	No	No