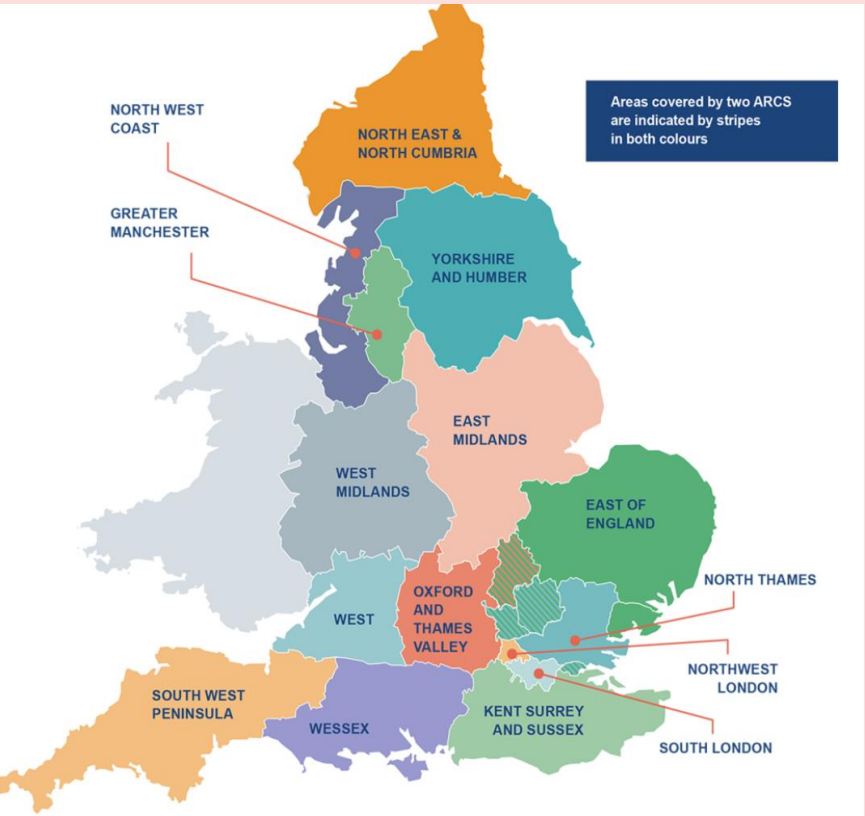
Notice for attendees: New call for NIHR Applied Research Collaborations



https://www.nihr.ac.uk/funding/nihr-applied-research-collaborations-arcs-2024/97016

- NIHR is launching a new open competition for infrastructure in applied health and care to designate and fund NIHR Applied Research Collaborations (ARCs) in England.
- Eligible NHS organisations may submit one application for funding up to £16.3m over five years from 1 April 2026.
- Purpose of the NIHR ARCs is **to undertake high-quality applied health, public health and social care research** with a **focus on generalisable learning at a regional and national level**. ….
- Currently across England there is a **network of 15 local ARC partnerships** between NHS providers, universities, charities, local authorities, Health Innovation Networks and other organisations, see https://www.nihr.ac.uk/about-us/what-we-do/infrastructure/applied-research-collaborations#one for details

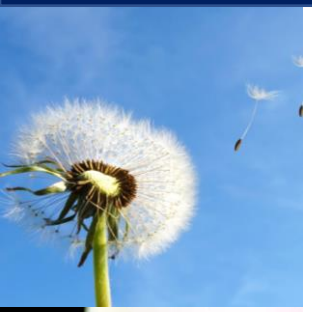
Role and Priorities of Future NIHR ARCs, 2026-31

Role

- Develop and conduct **high quality, generalisable**, **applied health, public health and social care research**
- Use **knowledge mobilisation approaches** to support an increase in the rate at which research findings are implemented into practice
- Address **health inequalities**
- Increase the country's **capacity and capability,** including in under-represented specialties and professions
- Collaborate to respond to national health and care challenges, **responding to DHSC and NHS England priorities**
- Contribute to **broader economic gain**
- Work collaboratively across NIHR infrastructure and the wider health and care system for progression towards **nationally generalisable evidence**

Priority areas of health and social care include:

- Major conditions such as dementia, diabetes, and risk factors for cardiovascular disease and cancer such as smoking, obesity
- Mental health, including better integration between mental and physical health services
- Children and young people's health
- Multiple long-term conditions
- Women's health
- Supporting delivery of health services in community and primary care and at home
- Prevention
- Supporting people living with long-term conditions into work and to remain in work
- Supporting the recovery of the health and care systems, including the health and wellbeing of the workforce
- Social care, including supporting people to live safely at home for longer



Mirtazapine to alleviate severe breathlessness in patients with COPD or ILD:

an international, multicentre, double-blind, randomised, placebo-controlled, phase 3 mixed-method trial (BETTER-B)

Professor Irene J Higginson, FRCP FFPHM PhD

On behalf of the BETTER-B consortium,

website *https://betterbreathe.eu*

Funding & Disclosures

European Union's Horizon 2020 research and innovation programme, grant agreement No 825319;
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Cicely Saunders International Breathlessness Programme;
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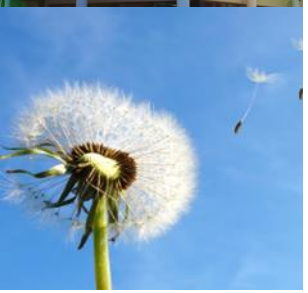

BETTER-B programme

BETTER-B

Cicely Saunders International
Better care at the end of life

KING'S College LONDON

International team including early career researchers and clinicians


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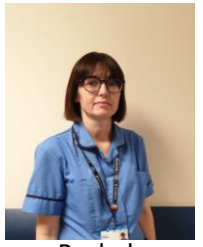
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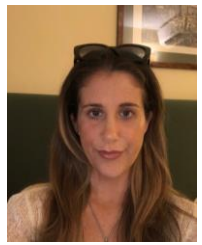
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See all partners: website https://betterbreathe.eu

Why is breathlessness important?

- Defined: A **subjective** experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity[1]
- Becomes **chronic** or **refractory** when it persists despite optimal treatment of the underlying pathophysiology and results in disability
- Also called dyspnoea/dyspnea
- **Affects 15 million people in the Europe, 75 million worldwide**, many more if families are included
- **Common** in advanced COPD,, heart failure, cancer, neurological other lung diseases
- Frequent **cause of** emergency hospital **admission** (1 in 5 ambulance presentations)[2]

1) Parshall MB et al. AJRCCM 2012
2) Hutchinson A, et al. BMC Pulm Med 2017; 17: 53
3) Holland AE et Eur Respir J 2024;
4) Simon ST, et al. CDSR 2010; 1: CD007354.pub2

Pharmacological management

- Opioids: limited evidence of small effect likely, concerns about long-term effects[3]
- Benzodiazepines: No benefit over placebo, possible adverse effects, small number of studies[4]

Mirtazapine: NaSSA

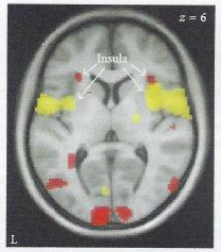
- Widely used in anxiety, panic disorder, major depressive disorders associated with anxiety.

- Antagonises receptors (α2, 5HT2A and 5HT2C)

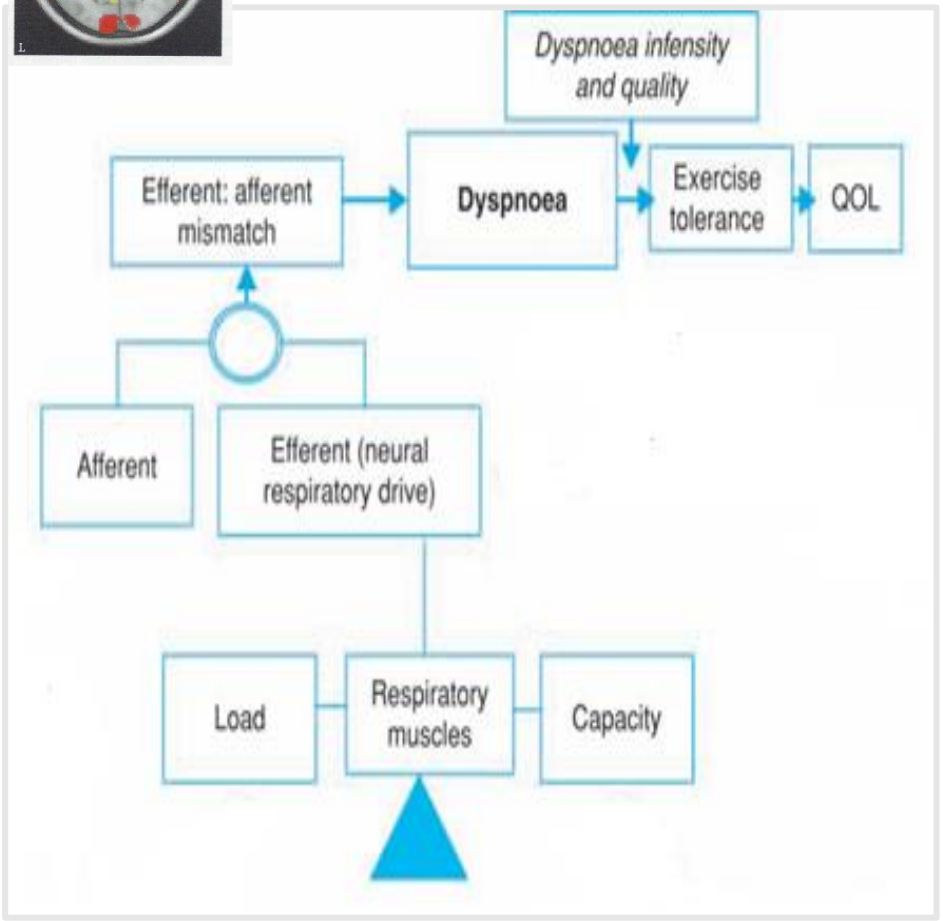
- Preferred over SSRIs due to quicker OoA, fewer side effects and drug interactions

- Appetite stimulation, anti-emetic, analgesic properties and weight gain could be of benefit to patients with advanced disease.

Why?: lack of treatments, biological feasibility, case reports + evidence of use of mirtazapine



Model of breathlessness as a balance between load and capacity



Pharmacological treatment strategies used:

- European survey, 450 responses
- Clinicians use **antidepressants** for breathlessness 'often or always'
- COPD – 19% respiratory physicians, 11% palliative care physicians
- fILD – 12%, 13%

Krajnik M, et al BMC Pulmonary Medicine. 2022 Jan;22(1):41

Feasibility study

A randomised, double-blind, multi-centre, feasibility trial of mirtazapine in adults with mMRC score of ≥3.

N = 64 patients: 30 in mirtazapine and 34 in placebo grp.

Results

No differences between arms for tolerability or safety

Worst breathlessness ratings day 28, 7.1 (95%CI 6.2-7.9, placebo), 6.3(95%CI 5.6-7.0, mirtazapine)

Higginson et al. Thorax 2020;75:176-179

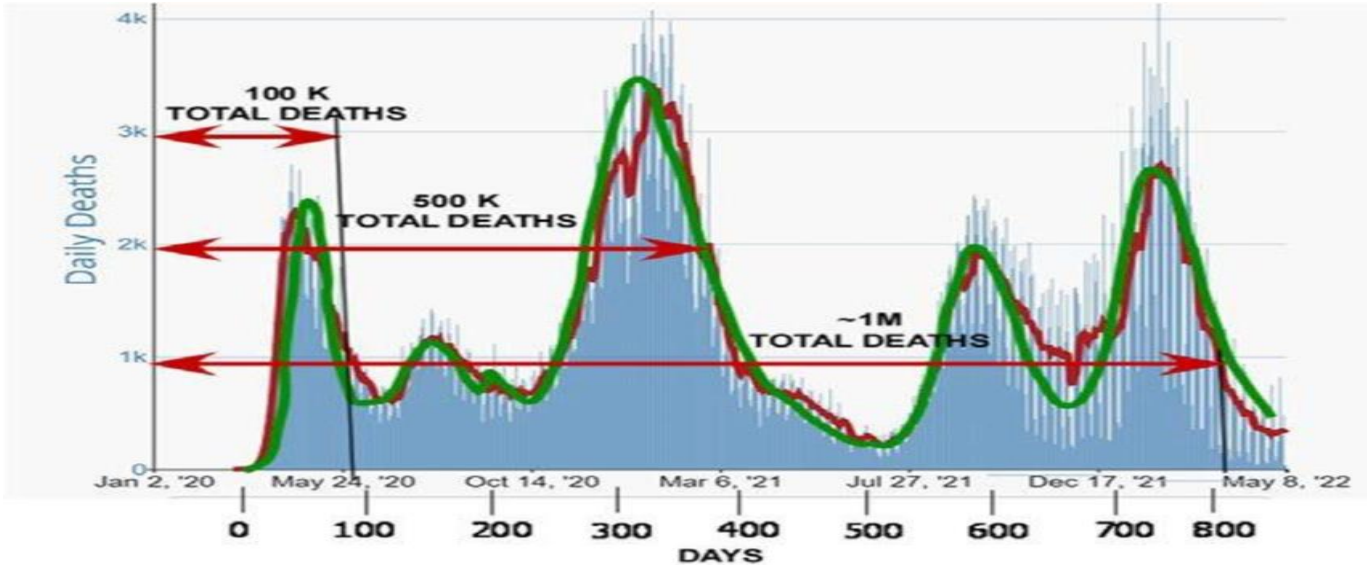
BETTER-B: International, multi-centre, randomised, placebo controlled, pragmatic, double-blind Phase 3 trial

Settings	16 centres in 7 countries
Participants	Adults with Chronic Obstructive Pulmonary Disease and/or Interstitial Lung Disease, Grade 3-4 modified MRC breathlessness scale
Intervention	Oral mirtazapine 15mg/day, escalated up to 45mg if no response, for 56 days
Control	Placebo, matched for appearance
Outcomes (day 0, 7, 14, 28, 56, 180)	Primary: 'Worst' breathlessness over the past 24 hours using numerical rating scale (day 56) Secondary: • 'average' breathlessness over the past 24 hours using numerical rating scale • Chronic Respiratory Questionnaire (CRQ) • Integrated Palliative care Outcome Scale (IPOS) • Hospital Anxiety and Depression Scale (HADS) • Qualitative interviews • Health care use Trial registration: ISRCTN10487976
Analysis	Modified intention-to-treat using multivariable multi-level repeated measures model

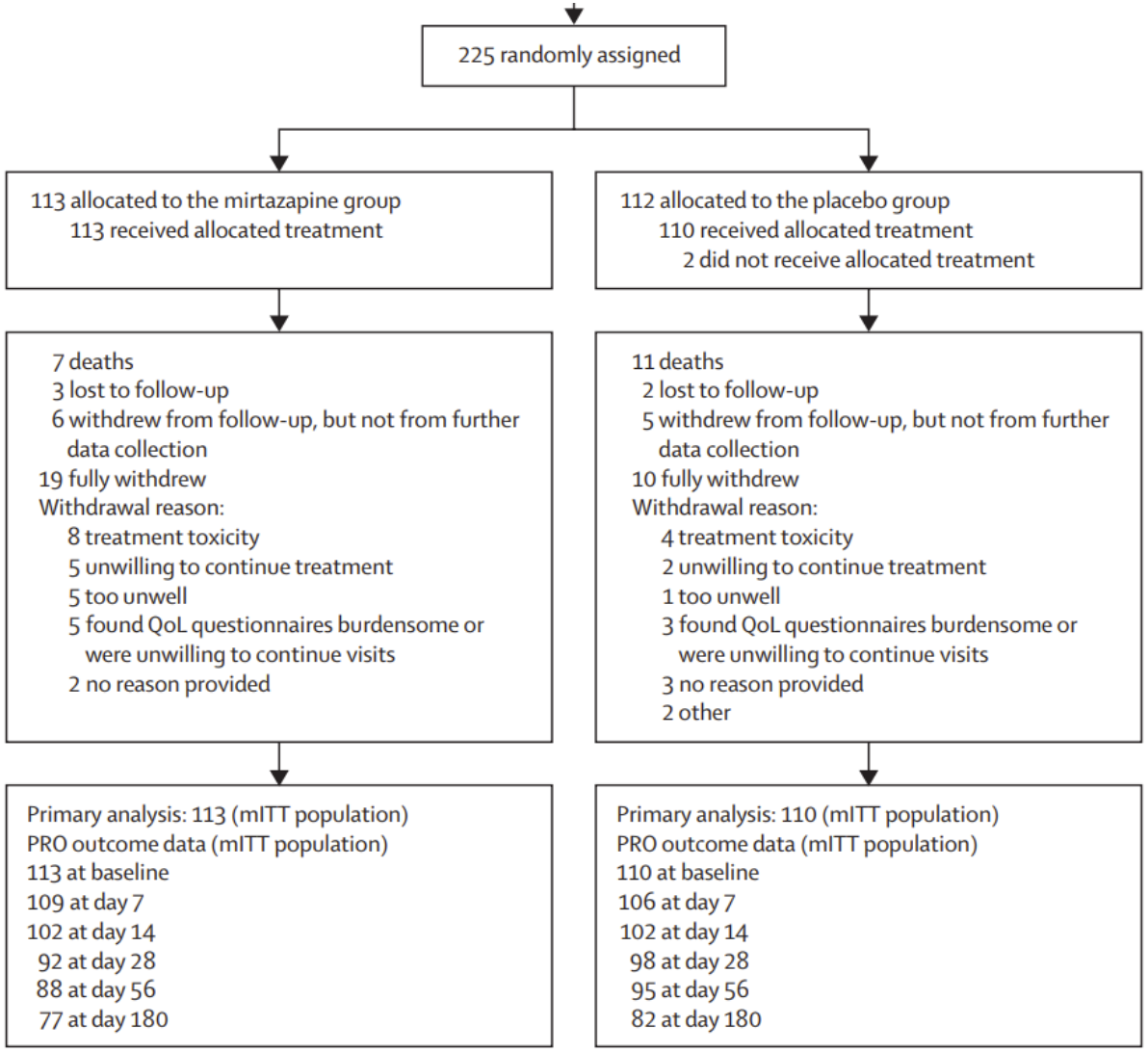
Higginson et al. 2024

Higginson IJ, et al. Lancet Respir Med. 2024 Oct;12(10):763-774; study website: https://betterbreathe.eu

Some '*unanticipated*' issues encountered while running BETTER-B

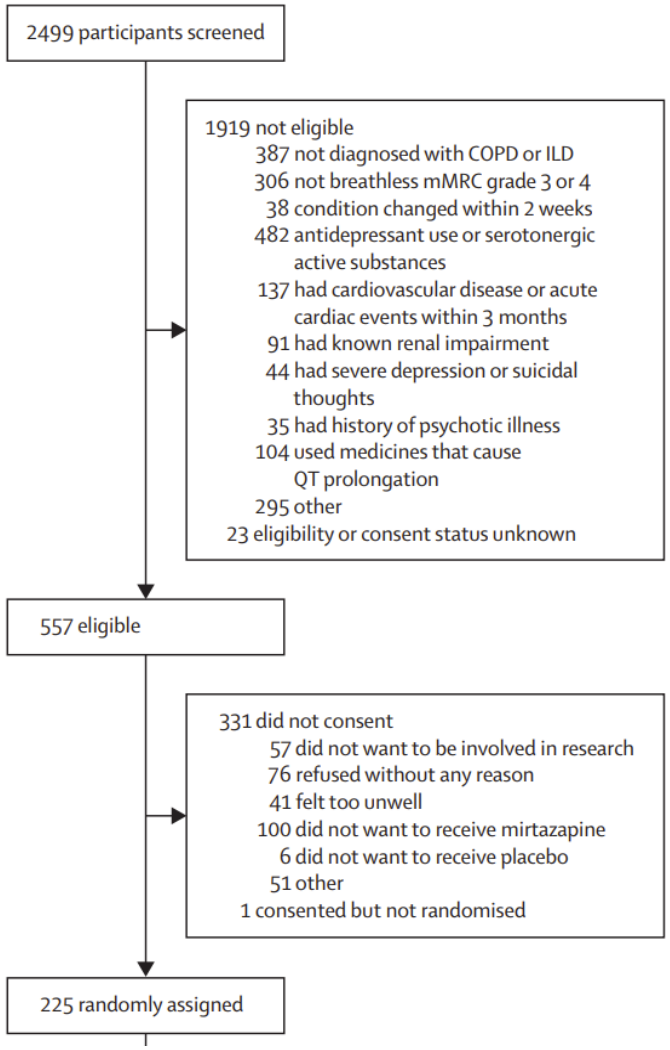


Trial profile: 225 randomly assigned



Plus 75 caregivers of participants were eligible and consented: 43 mirtazapine, 32 placebo.

31 qualitative interviews; 23 with participants (11 mirtazapine, 12 placebo) and 8 with caregivers.



Higginson IJ, et al. Lancet Respir Med. 2024 Oct;12(10):763-774.

Participants & Attrition

When we analysed this we were blinded, so saw group 1 and group 2

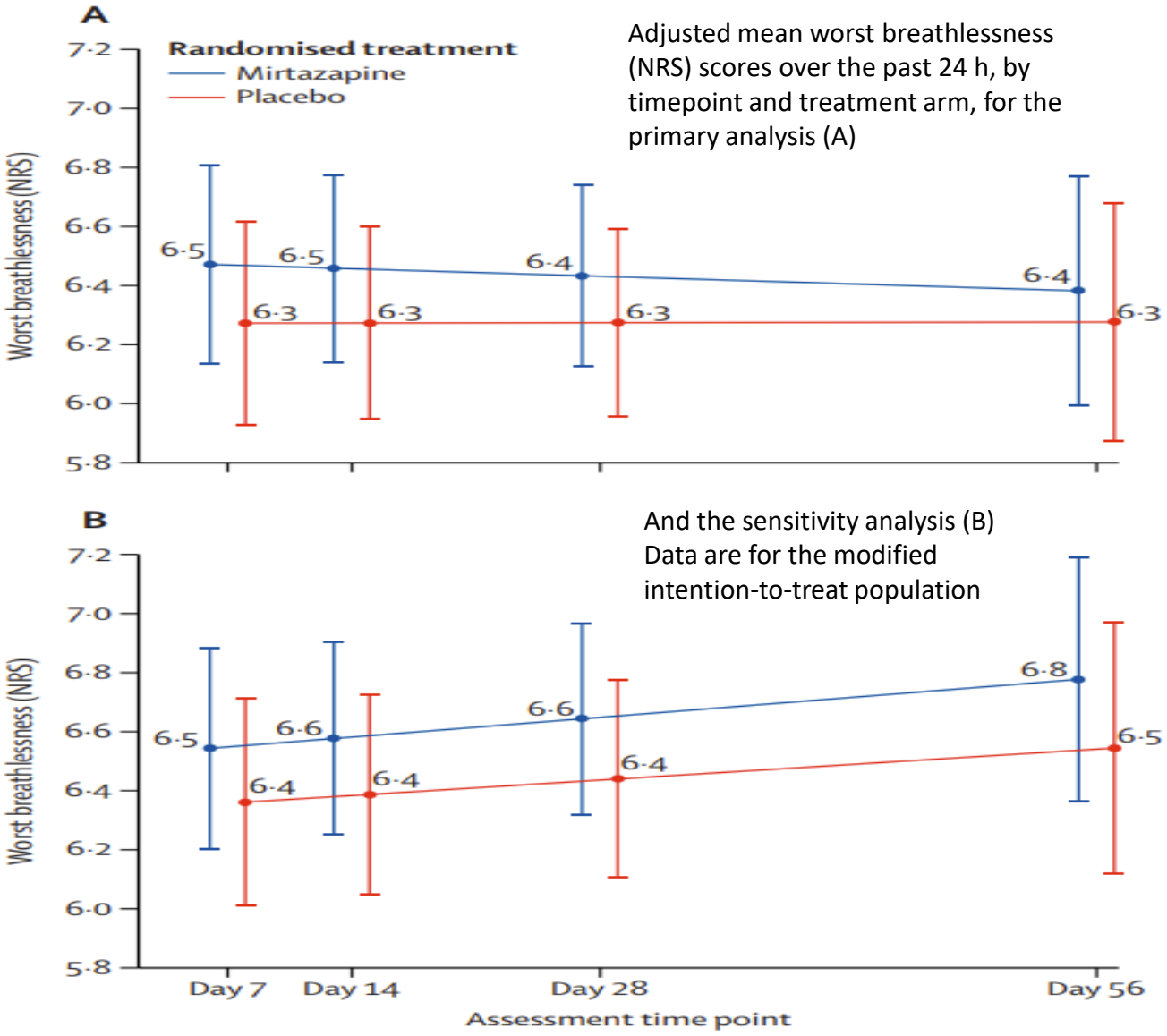
	Mirtazapine (n=113)	Placebo (n=112)	Total (n=225)
Age (years)			
Mean (s.d.)	72·8 (8·91)	71·7 (8·95)	72·2 (8·93)
Gender			
Male	73 (64·6%)	75 (67·0%)	148 (65·8%)
Female	40 (35·4%)	37 (33·0%)	77 (34·2%)
Primary diagnosis			
COPD	63 (55·8%)	61 (54·5%)	124 (55·1%)
ILD	50 (44·2%)	51 (45·5%)	101 (44·9%)
HADS anxiety score			
≤10	89 (78·8%)	88 (78·6%)	177 (78·7%)
>10	24 (21·2%)	24 (21·4%)	48 (21·3%)
HADS depression score			
≤10	88 (77·9%)	88 (78·6%)	176 (78·2%)
>10	25 (22·1%)	24 (21·4%)	49 (21·8%)
Taking opioids			
Yes	19 (16·8%)	17 (15·2%)	36 (16·0%)
No	94 (83·2%)	95 (84·8%)	189 (84·0%)
mMRC grade			
Grade 3	75 (66·4%)	74 (66·1%)	149 (66·2%)
Grade 4	38 (33·6%)	38 (33·9%)	76 (33·8%)
Comorbidities			
Yes	95 (84·1%)	86 (76·8%)	181 (80·4%)
No	18 (15·9%)	26 (23·2%)	44 (19·6%)

Higginson IJ, et al. Lancet Respir Med. 2024 Oct;12(10):763-774; study website: https://betterbreathe.eu

	Mirtazapine (n=113)	Placebo (n=110)	Total (n=223)
Day 7			
Worst breathlessness (NRS) score collected	109 (96·5%)	106 (96·4%)	215 (96·4%)
Missed questionnaire	1 (0·9%)	0 (0·0%)	1 (0·4%)
ADI (attrition due to illness)	2 (1·8%)	1 (0·9%)	3 (1·3%)
AAR (attrition at random)	1 (0·9%)	3 (2·7%)	4 (1·8%)
Day 14			
Worst breathlessness (NRS) score collected	103 (91·2%)	102 (92·7%)	205 (91·9%)
Missed questionnaire	3 (2·7%)	1 (0·9%)	4 (1·8%)
ADI (attrition due to illness)	3 (2·7%)	4 (3·6%)	7 (3·1%)
AAR (attrition at random)	4 (3·5%)	3 (2·7%)	7 (3·1%)
Day 28			
Worst breathlessness (NRS) score collected	93 (82·3%)	99 (90·0%)	192 (86·1%)
Missed questionnaire	3 (2·7%)	1 (0·9%)	4 (1·8%)
ADD (attrition due to death)	3 (2·7%)	0 (0·0%)	3 (1·3%)
ADI (attrition due to illness)	8 (7·1%)	6 (5·5%)	14 (6·3%)
AAR (attrition at random)	6 (5·3%)	4 (3·6%)	10 (4·5%)
Day 56			
Worst breathlessness (NRS) score collected	88 (77·9%)	93 (84·5%)	181 (81·2%)
Missed questionnaire	2 (1·8%)	3 (2·7%)	5 (2·2%)
ADD (attrition due to death)	3 (2·7%)	1 (0·9%)	4 (1·8%)
ADI (attrition due to illness)	12 (10·6%)	6 (5·5%)	18 (8·1%)
AAR (attrition at random)	8 (7·1%)	7 (6·4%)	15 (6·7%)

Primary outcome and secondary outcomes

(Blinding continued until after agreed interpretation)



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

Secondary outcomes:

No differences for: average NRS breathlessness score, Chronic Respiratory Questionnaire (CRQ) subscales, palliative symptoms (Integrated Palliative care Outcome Scale, IPOS), anxiety and depression (HAD), episodes of breathlessness, Australia-modified Karnofsky performance scale, generalised self-efficacy scale.

Higginson et al. 2024

Higginson IJ, et al. Lancet Respir Med. 2024 Oct;12(10):763-774; study website: https://betterbreathe.eu

Adverse Reactions and Care Provision

	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%)

Care provision (mean (SD)):

Acute hospital nights

0·99 (4·4) mirtazapine, 0·48 (2·1) placebo

Outpatient visits

1·66 (2·6) mirtazapine, 1·32 (2·0) placebo

Hours of family care

72·90 (153·3) mirtazapine, 58·46 (142·7) placebo

Higginson IJ, et al. Lancet Respir Med. 2024 Oct;12(10):763-774; study website: https://betterbreathe.eu

BETTER-B Practice review: Pharmacological management of severe chronic breathlessness in adults with advanced life-limiting diseases

KING'S College LONDON

Aim: To provide practice recommendations on the safe use of medications for severe chronic breathlessness.

Design: Scoping review of (inter)national guidelines and systematic reviews. Primary studies included where no systematic review could be identified. Consensus reached by 75% approval within an international expert panel.

Data sources: MEDLINE, Cochrane Library and Guideline International Network until March 2023. Included publications on antidepressants, benzodiazepines, opioids or corticosteroids for chronic breathlessness in adults with cancer, COPD, ILD or CHF.

Results: Evidence from 8 guidelines, 14 sys reviews and 3 RCTs on antidepressants is limited. Low quality evidence favouring opioids in COPD, cancer and ILD patients. For CHF, evidence is inconclusive. Benzodiazepines should only be considered for anxiety associated with severe breathlessness. Antidepressants and corticosteroids should not be used.

Simon et al 2024

Simon ST, Higginson IJ, et al Palliat Med. 2024 Sep 12, doi:10.1177/02692163241270945

Take home messages from BETTER-B

- We can conclude, with 95% confidence, that mirtazapine of doses 15-45mg daily over 56 days does not improve severe breathlessness among patients with COPD or ILD
- Further, it might cause adverse reactions and increase care use
- It is not recommended to alleviate severe breathlessness
- Urgent need for rigorous pragmatic clinical trials in assessing potential treatments for severe breathlessness, ensuring not only efficacy but also safety and lessened healthcare 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 disease remains paramount

Higginson IJ, et al. Lancet Respir Med. 2024 Oct;12(10):763-774; study website: https://betterbreathe.eu

Acknowledgements

- BETTER-B patients and caregivers
- BETTER-B Patient and Public Involvement (PPI) group members
- Funders: European Union's Horizon 2020 research and innovation programme, grant agreement No 825319; The National Health and Medical Research Council (NHMRC) (Australia); Cicely Saunders International Breathlessness Programme; NIHR Applied Research Collaboration South London
- BETTER-B sites across the UK, Europe, New Zealand and Australia
- BETTER-B independent critical friends and advisors including Professor Giovanni Apolone, the late Professor Randall Curtis, Professor Daisy J.A. Janssen and Professor Michael Kreuter.
- BETTER-B independent Data Monitoring and Safety Committee (DMSC) led by Professor Magnus Ekstrom; Trial Steering Committee (TSC) led by Dr Brian Cassel; Ethics Advisory Board led by Professor Bobbie Farsides and the Trial Management Group (TMG)

study website: https://betterbreathe.eu

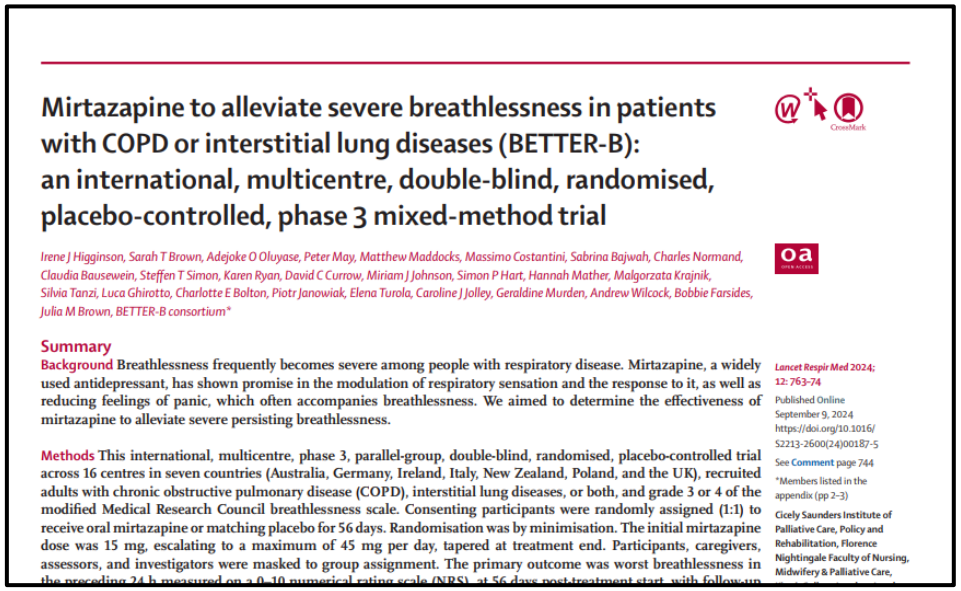
BETTER-B Partners and Consortium

Australia and New Zealand

- Calvary Healthcare Kogarah (Australia)
- Barwon Health (Australia)
- University of Technology, Sydney (Australia)
- Westmead Hospital, Sydney (Australia)
- Christchurch Hospital (New Zealand)

Europe

- Klinikum Der Universitaet Zu Koeln (Germany)
- Ludwig-Maximilians-Universitaet Muenchen (Germany)
- Trinity College Dublin, Ireland
- University College Dublin (Ireland)
- Azienda Unita Sanitaria Locale IRCCS di Reggio Emilia (Italy)
- Universita Cattolica Del Sacro Cuore (Italy)
- Gdanski Uniwersytet Medyczny (Poland)
- Uniwersytet Mikolaja Kopernika W Toruniu (Poland)
- European Respiratory Society and European Lung Foundation, (Switzerland)
- King's College London (UK)
- The University of Nottingham and Nottingham University Hospitals NHS Trust (UK)
- University of Leeds (UK)



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

Irene J Higginson, Sarah T Brown, Adejoke O Oluyase, Peter May, Matthew Maddocks, Massimo Costantini, Sabrina Bajwah, Charles Normand, Claudia Bausewein, Steffen T Simon, Karen Ryan, David C Currow, Miriam J Johnson, Simon P Hart, Hannah Mather, Malgorzata Krajnik, Silvia Tanzi, Luca Ghirotto, Charlotte E Bolton, Piotr Janowiak, Elena Turola, Caroline J Jolley, Geraldine Murden, Andrew Wilcock, Bobbie Farsides, Julia M Brown, BETTER-B consortium*

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

Lancet Respir Med 2024; 12: 763–74

Published Online September 9, 2024 https://doi.org/10.1016/S2213-2600(24)00187-5

See Comment page 744

*Members listed in the appendix (pp 2–3)

Cicely Saunders Institute of Palliative Care, Policy and Rehabilitation, Florence Nightingale Faculty of Nursing, Midwifery & Palliative Care,

Dr Emma Grainger, Editor-in-Chief, *The Lancet Respiratory Medicine*

Why we selected this paper for external peer review:

- Severe breathlessness is a relevant major and global problem.
- Well designed and executed phase 3 randomised controlled trial.
- Substantial off label use of mirtazapine and growing interest, despite the limited evidence.
- Study had implications for future care and could lead to a change in practice.
- Increased healthcare use and increased adverse reactions with intervention.
- Important negative trial in an area of unmet need.

THE LANCET Respiratory Medicine