An evidence-based policy brief

Insights from the international BETTER-B study: the anti-depressant Mirtazapine does not alleviate severe breathlessness and has implications for off-label medications in Palliative Care.

Key Findings

Mirtazapine does not improve severe breathlessness in patients with Chronic Obstructive Pulmonary Disease (COPD) and/or Interstitial Lung Disease (ILD) when compared with placebo

It might cause side effects and increase the need for informal care and formal healthcare, including hospital admissions, compared with placebo.

These findings are likely to be relevant to individuals with a wider range of diseases including cancer, heart disease and long COVID.

The use of off-label medicines by recommending a medicine be used for a purpose beyond its licence is common in advanced illness and palliative care because there are few licenced and tested medicines to treat symptoms. The research's findings raise wider issues about the efficacy and ethical implications of using medicines off-label, without them having been subject to a rigorous evaluation framework.

The findings also highlight that clinical trials for symptom management are urgently needed.

Policy Recommendations

- Based on current research, mirtazapine should not be used to alleviate severe breathlessness for people with COPD or ILD.
- Based on existing best evidence, early identification and non-pharmacological approaches, such as those offered by pulmonary rehabilitation and breathlessness support services, should be the first line treatment for severe breathlessness. These should include an appropriately personalised approach. Such services should be prioritised and supported as they are not universally available.
- There is an urgent need to find more effective treatments for severe breathlessness. Rigorous, pragmatic clinical trials into potential treatments, considering efficacy, safety and healthcare burden are vital.

- Guidelines should be very cautious about recommending any medicines based on only clinical experience or case series as these may overestimate possible benefits.
- Individual clinicians should be cautious when recommending or prescribing off-label treatments to control symptoms, should monitor effects and possible side effects carefully.

Why is this research important?

Chronic respiratory diseases affect 454.6 million people worldwide, with numbers predicted to increase. Over 217 million people globally have Chronic Obstructive Pulmonary Disease (COPD) or Interstitial Lung Disease (ILD) which commonly have severe breathlessness as a major symptom that increases as the disease progresses.

There are significant clinical challenges and personal impacts associated with severe breathlessness. Despite this, there are currently no licensed medicines for severe breathlessness globally, other than, in Australia, the use of regular low-dose sustained-release morphine for chronic breathlessness.

Mirtazapine, a widely used antidepressant, showed promise. This programme, called BETTER-B, tested its efficacy to relieve severe breathlessness in COPD and ILD.[1]

We conducted in 2019 a survey across Europe and found that some clinicians were already recommending antidepressants off-label to manage breathlessness.[2] Of respiratory medicine (RM) and palliative care (PC) physicians responding to the survey, 19% of RM and 11% of PC physicians often or always recommended antidepressants for breathlessness in patients with advanced COPD, even where there was no evidence of depression, while in fibrotic ILD the percentages were 12% and 13% respectively.

Published in Lancet Respiratory Medicine,[1] BETTER-B trial represents the first comprehensive evaluation of mirtazapine's effectiveness, safety and healthcare utilisation in managing severe chronic breathlessness in patients with respiratory diseases.

The finding that mirtazapine is not effective is noteworthy, not only to prevent its continued use, but also for the wider questions it raises about the use of off-label medicines.

What did we do?

We conducted an international, multicentre phase 3 parallel group, double-blind, randomised placebo-controlled trial across 16 centres in seven countries, recruiting adults with COPD and/or ILD, to assess the efficacy of mirtazapine in controlling severe breathlessness. Secondary objectives included assessing quality of life, healthcare use and patient and carer qualitative reports.

Patient and Public Involvement and Engagement (PPIE) was integrated at all stages of the study through a specific group, and partnership with the European Lung Foundation.

What did we find?
Contrary to the team's initial hypothesis, administration of mirtazapine in specific doses for nearly 2 months did not yield significant benefits compared to placebo. Similar results were observed for secondary measures such as quality of life, broader symptoms, anxiety and depression, and frequency of breathlessness episodes.

In contrast, patients treated with mirtazapine experienced slightly more side effects and needed slightly more care from hospital and from their family members than did those receiving placebo.

Insights from qualitative interviews with patients and caregivers during the study highlighted the persistent challenges of breathlessness. These firsthand accounts underscore the importance of patient-centred care in respiratory medicine.

These findings, along with those from another study trialling the antidepressant sertraline, which did not alleviate chronic breathlessness,[3] raises doubts about the effectiveness of this group of medicines for severe breathlessness in people with respiratory diseases.

It emphasises the necessity of conducting clinical trials to evaluate therapies for severe symptoms like breathlessness, rather than relying on anecdotal or small non-comparative studies that can overstate therapeutic benefits.

It also draws attention to the risks associated with off-label prescribing, where clinicians, while intending to help, may inadvertently cause side effects and increase the need for care.

It recommends a focus on holistic non-pharmacological approaches that have a strong evidence-base, such as those offered by pulmonary rehabilitation and breathlessness support services, underpinned by early identification, as first-line treatments.

Key resources
The BETTER-B Trial results are published in The Lancet Respiratory Medicine.

BETTER-B website: https://betterbreathe.eu/

BETTER-B Survey: Do guidelines influence breathlessness management in advanced lung diseases? A multinational survey of respiratory medicine and palliative care physicians | BMC Pulmonary Medicine | Full Text (biomedcentral.com)

GOLD 2024 guideline: https://goldcopd.org/2024-gold-report/

Managing breathlessness
Managing breathlessness - European Lung Foundation
Managing breathlessness in advanced illness | Feature from King's College London (kcl.ac.uk)

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References

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3. Currow DC, Ekstrom M, Louw S, et al. Sertraline in symptomatic chronic breathlessness: a double blind, randomised trial. *Eur Respir J* 2019; **53**(1): 1801270.