Brief for Clinicians

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

KEY MESSAGES

The International BETTER-B randomised trial has revealed that despite initial promise and biological plausibility doses ranging from 15 to 45mg of mirtazapine failed to alleviate severe breathlessness among individuals with advanced respiratory diseases. Mirtazapine should therefore not be used for this purpose.

Additionally, mirtazapine might lead to adverse effects and escalate the costs from formal healthcare, including hospital admissions, as well as the burdens on informal caregivers.

When managing breathlessness in advanced diseases, clinicians are advised to prioritise early identification and non-pharmacological interventions, such as those provided by holistic pulmonary rehabilitation and breathlessness support services.

BETTER-B findings underscore the importance of subjecting medicines in palliative care to rigorous randomised controlled trials. It is crucial that the use of unlicensed off-label medicines should be approached with caution, in line with the ethical principle of 'do no harm'.

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) and Interstitial Lung Disease (ILD) which commonly have severe breathlessness as a major symptom that increases as the diseases progresses. There are substantial clinical challenges, personal impact and health care costs associated with such severe breathlessness.

Despite this, there are currently no licensed medicines for persistent and severe breathlessness globally, other than, in Australia, the use of regular low-dose sustained-release morphine.

Mirtazapine, a widely used antidepressant, showed promise. The BETTER-B study tested its effectiveness to relieve severe breathlessness among people with COPD or ILD.

This study, whose findings are published in Lancet Respiratory Medicine,[1] represents the first comprehensive evaluation of mirtazapine's effectiveness and safety in managing severe breathlessness.

Given the lack of licensed medicines, clinicians understandably want to do something for their patients and so turn to 'off-label' prescribing, i.e. recommending a medicine in a manner different from its licence. Clinicians caring for people with advanced lung diseases often face this scenario because the only licenced medicines in Europe and many other countries for managing severe breathlessness are those designed to treat the underlying illness.

When these medications lose effectiveness, the only pharmacological options left are off-label treatments. Off-label medicine usage is common in palliative care and advanced illness, constituting approximately one-third of prescriptions. It is particularly pronounced in breathlessness care.

A survey of respiratory (RM) and palliative care (PC) physicians was undertaken in 2019 as part of the BETTER-B programme.[2] Of those that responded, 19% of RM and 11% of PC physicians often or always recommended antidepressants for patients with advanced COPD , even where there was no evidence of depression, while in fibrotic ILD the percentages were 12% of RM physicians and 13% of PC physicians.

This demonstrates the vital need for proper evaluation of medicines.

What did we do?
We conducted an international, multicentre phase 3 double-blind, randomised placebo-controlled trial across 16 centres in seven countries recruiting adults with COPD and/or ILD to assess the effectiveness of mirtazapine in alleviating severe breathlessness. Secondary objectives included assessing quality-of-life, patient symptoms, healthcare use and patient and carer qualitative reports.[1]

Patient and Public Involvement and Engagement (PPIE) was integrated at all stages through a specific group, and partnership with the European Lung Foundation and members of the Cicely Saunders Institute online forum.

BETTER-B stands as the largest trial in the world targeting individuals severely affected by breathlessness, i.e. need to stop for breath after walking ~100 meters or after few minutes on the level or too breathless to leave the house, or breathless when dressing or undressing. Participants received either mirtazapine or placebo for 56 days, and were followed for 180 days.

What did we find?
We enrolled and randomly assigned 225 eligible participants with COPD or ILD and severe breathlessness. Contrary to our initial hypothesis, administering mirtazapine in doses ranging from 15 to 45 mg over 56 days did not yield significant benefits compared to placebo. This finding held true with 95% confidence in both the main analysis and sensitivity analysis. Secondary outcomes, including quality of life, broader symptoms, anxiety and depression, and frequency of breathlessness episodes, showed similar results. Additionally, the mirtazapine group exhibited slightly higher levels of side effects, increased hospital admissions, and greater caregiving demands for informal caregivers and family members.

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 and palliative care.

The study also found that access to effective non-pharmacological treatments, such as those offered by pulmonary rehabilitation and breathlessness support services varied between countries and centres, suggesting ways that routine care for people with breathlessness could be improved.

The study concluded that mirtazapine should not be used to alleviate breathlessness. Taken together the findings from the trial by Currow et al, which did not find benefits of sertraline,[3] it concludes that neither antidepressant is recommended and raises doubts about the effectiveness of antidepressants as a group of medicines to alleviate severe breathlessness in people with respiratory diseases.

Recommendations

- 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.
- Based on current research, mirtazapine or sertraline should not be used to alleviate severe breathlessness for people with COPD or ILD.
- Clinicians should advocate for more research into the effectiveness and safety of new medicines to alleviate breathlessness and other symptoms in palliative care and respiratory medicine. Clinicians should be cautious when recommending or prescribing treatments and medicines off-label and ensure appropriate evaluation if these are offered. If the patient experiences adverse or side effects, they should be cautious in assuming that these are due to disease progression.

Key resources

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

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

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

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/

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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.