



## Patient and carer brief

**A research programme has found that an antidepressant did not help long-term breathlessness. The BETTER-B project looked at the antidepressant mirtazapine. The findings have raised questions about using medicines in a manner different from its licence.**

### **Why was the research done?**

Long-term lung 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).

Severe breathlessness, becoming worse as the diseases progress, is very common in people with COPD and ILD as well as in other diseases such as cancer, heart disease and long COVID.

Unfortunately, there are currently no licensed medicines for long-term or severe breathlessness globally, except in Australia, where morphine can be used for long-term breathlessness. Therefore, there is an urgent need to find better treatments.

Given the lack of licensed medicines, clinicians often turn to 'off-label' prescribing, recommending a medicine in a manner different from its licence. This is common for controlling symptoms in advanced lung diseases. The only licensed medicines for severe breathlessness in most countries treat the underlying illness. When these lose effectiveness, off-label medicines are the only medicines left to try.

A survey of lung and palliative care physicians, as part of the BETTER-B programme, found that 19% of lung and 11% of palliative care physicians already often or always recommended antidepressants for advanced COPD, even without signs of depression. For fibrotic ILD, the figures were 12% and 13%, respectively.

This demonstrated the vital need for proper evaluation of possible treatments, like antidepressants, which are sometimes being used off-label.

### **What did we do?**

Mirtazapine, a widely used antidepressant, showed promise and so the BETTER-B research tested if it could relieve severe breathlessness in COPD and ILD compared with a dummy drug, known as a placebo. This was done through the international randomised trial, BETTER-B. Patients and carers were involved in and advised on the research processes from beginning to end.

We enrolled and randomly assigned 225 eligible adults with COPD or ILD and severe breathlessness across 16 centres in seven countries.

### **What were the results?**

There was no difference in severe breathlessness between those people taking mirtazapine and those taking placebo during the main period of the trial, of 56 days.

Similar results were found for other measures. This included a person's quality of life, broader symptoms, anxiety and depression, and frequency of breathlessness episodes. There were no differences found up to six months after the start of the trial.

In contrast, some people treated with mirtazapine experienced slightly more side effects and needed slightly more care from hospitals and from their family members than those receiving placebo during the first two months of treatment.

We also carried out in-depth interviews with people with severe breathlessness and their carers or family members to better understand their experiences. Some people described their symptoms changing without a clear pattern of improvement. Many did not notice any changes in their health, including sleep, appetite, mood, and drowsiness. Two people reported positive effects on their 'chest' symptoms, especially in the morning. Some experienced mild side effects like dizziness, memory problems, or dry mouth.

These interviews highlighted the persistent challenges of breathlessness faced day to day. These firsthand accounts highlight the importance of person-centred care for people living with lung diseases or receiving palliative care. Other information collected during the study on wider symptoms and effects demonstrates the complex and long-lasting symptoms and problems experienced by people with severe breathlessness.

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. This is another area of routine care that could be improved for people with breathlessness.

### **What wider questions were raised for patients and carers?**

Mirtazapine was being used 'off-label', meaning it was not originally developed to treat breathlessness and had not, along with other off-label medicines, been tested through sufficient clinical trials to enable it to be licenced.

However, people with severe breathlessness and their carers should be aware and informed about the medicines they are being offered and the alternatives, including the non-pharmacological alternatives.

Studies that show that a medicine is no better a treatment than another medicine or placebo are worth carrying out so that important questions about their effect can be answered.

## Recommendations

- Given the findings of the study we do not recommend mirtazapine as a treatment for severe breathlessness in COPD or ILD.
- Our findings shine light on the long-lasting, complex and changing nature of breathlessness, which requires a person-centred approach.
- From the study and our earlier survey, we recommended that people with severe breathlessness and COPD and ILD should be found early, and offered effective non-pharmacological treatments, such as those offered by pulmonary rehabilitation and breathlessness support services. These already have a good evidence base, especially when used in a timely way, and are already recommended in leading guidance.
- Pulmonary rehabilitation and breathlessness support services often offer an approach tailored to individual needs, including information, physical muscle strengthening or exercise, tips on how to breathe better, manage a severe episode of breathlessness, and plan any activities, however small, to give more personal control over breathlessness.
- We also recommend that you ask about the evidence for any medicine offered especially if it is off-label.
- If you decide to try an off-label medicine, do monitor whether you think it helps or not, and be aware of any new symptoms. Do not assume they are just because your disease is progressing. They might be side-effects of medication.
- Ideally off-label medicines should be tested in proper evaluations, such as the BETTER-B trial, so that benefits and side effects can be properly evaluated.
- Research into symptomatic treatments for severe breathlessness is urgently needed, with advocacy for such research.

## 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 \(biomedcentral.com\)](#)

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