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## **Abstract**

### **Background**

Breathlessness remains a common and distressing symptom in people with advanced disease with few effective treatment options. Repurposing of existing medicines has been effective in other areas of palliative care, for example antidepressants to treat pain, and offers an opportunity to deliver improved symptom control in a timely manner. Previous case series have shown reduced breathlessness following the use of sertraline (a selective serotonin reuptake inhibitor) in people with chronic obstructive pulmonary disease.

### **Cases**

Six cases where mirtazapine, a noradrenergic and specific serotonergic antidepressant, was used to treat chronic breathlessness in advanced lung disease.

### **Case management**

All cases received mirtazapine at a starting dose of 15mg, prescribed under the care of their primary care physician.

### **Case outcome**

All cases reported less breathlessness and being able to do more. Some cases also reported beneficial effects on anxiety, panic, appetite and sleep. Cases had been receiving mirtazapine for a variable time period (2 weeks to 5 months) at the time of the interviews. No adverse effects were reported.

### **Discussion**

Patients with chronic breathlessness in this case series reported benefits during mirtazapine treatment. To determine the effectiveness of mirtazapine in alleviating breathlessness and improving quality of life in chronic lung disease, blinded randomised trials are warranted.

### **Key words**

Breathlessness, shortness of breath, mirtazapine, antidepressant, case series, advanced disease

## **Key Statements**

### **What is already known about the topic?**

- Breathlessness is a common and distressing symptom in advanced disease, with few effective treatment options
- New treatments are urgently needed
- Repurposing of existing medicines has been effective in other areas of palliative care and offers a potential opportunity to deliver improved symptom control in a timely manner

### **What this paper adds**

- This case series is the first to report the use of mirtazapine in the management of chronic breathlessness
- Patients with advanced lung disease and chronic breathlessness reported mirtazapine to be of benefit to them
- Patients reported less breathlessness and being able to do more, as well as beneficial effects on anxiety, panic, appetite, and sleep

### **Implications for practice, theory or policy**

- In this case series beneficial effects were reported when patients with chronic lung disease and severe breathlessness were treated with mirtazapine
- However, to determine the effectiveness of mirtazapine in alleviating breathlessness and improving quality of life in patients with chronic lung disease, blinded randomised trials are warranted
- Choice of outcome measures which incorporate not only breathlessness, but anxiety, panic, appetite and sleep will be important when conducting a trial

## Background

Breathlessness is a common and distressing symptom in people with advanced malignant and non-malignant disease<sup>1</sup>. Chronic breathlessness has recently been defined as breathlessness at rest or on minimal exertion that persists despite optimal treatment of the underlying disease<sup>2</sup>.

Whilst the current evidence-base for individual non-pharmacological interventions is variable, a multidisciplinary approach combining a number of components (pacing, breathing training and use of a hand-held fan) has been shown to be effective at improving confidence and control over breathing<sup>3</sup>. There are few effective pharmacological treatment options, with some evidence to support use of opioids, but concerns regarding side effects and small effect sizes, and no evidence for benzodiazepines<sup>4</sup>. New treatments are urgently needed. Repurposing existing medicines has been effective in other areas of palliative care (for example antidepressants to treat pain) and offers a potential opportunity to deliver improved symptom control in a timely manner.

Two case series of sertraline, a selective serotonin reuptake inhibitor (SSRI), showed a subjective decrease in breathlessness in patients with chronic obstructive pulmonary disease (COPD)<sup>5,6</sup>, and a phase III trial is ongoing to determine effectiveness to alleviate chronic breathlessness in advanced illness<sup>7</sup>. SSRIs inhibit serotonin re-uptake resulting in a rise in serotonin (5HT) which is thought to create their therapeutic effect in depression<sup>8</sup>. The mechanism of action of SSRIs in breathlessness is not understood. Serotonin may partially modulate respiratory function, and impact on areas of the brain relating to fear and anxiety, which appear to be more active during experimentally induced breathlessness<sup>8</sup>.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA), and enhances 5-HT<sub>1</sub> receptor mediated neurotransmission resulting in increased levels of serotonin in the cortex<sup>8</sup>. Increased serotonin may be beneficial in the treatment of chronic breathlessness by inhibiting 'fear circuits' which have been shown to originate in the amygdala, and appear to be more active during experimentally induced breathlessness<sup>8</sup>. Respiratory modulation is another possible mechanism as described above. Mirtazapine is an effective treatment for depression, with a faster onset of action when compared to SSRIs. A number of small randomised controlled trials have evaluated efficacy in anxiety disorders, with some evidence in the treatment of panic disorder<sup>9</sup>. These effects may be of additional benefit in breathlessness in chronic lung disease which has been associated with high levels of anxiety. Mirtazapine blocks 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors, which can be an advantage in clinical practice by reducing the gastrointestinal effects commonly reported with SSRIs<sup>8</sup>. At lower doses mirtazapine can be quite sedating due to its high affinity for histamine H<sub>1</sub> receptors; but at higher doses the increased noradrenergic transmission counteracts this effect<sup>8</sup>. The most common

side effects of mirtazapine are increased appetite, weight gain and somnolence, which may be advantageous to patients with advanced disease who frequently report poor appetite and disrupted sleep<sup>1</sup>.

### **Case presentation**

We present a case series of 6 people who received mirtazapine for breathlessness at a starting dose of 15mg, prescribed under the care of their primary care physician. All had recently participated in a randomised controlled feasibility trial of mirtazapine for chronic breathlessness, and had requested continued compassionate use. Qualitative interviews were conducted as part of the feasibility trial. Data was collected between March 2017 and February 2018. The study received ethical approval through the London Central Research Ethics Committee (REC reference 16/LO/0091). All patients entered the trial voluntarily and provided written consent for their anonymised data to be shared in scientific publications. The trial enrolled people with advanced disease and severe breathlessness, as indicated by a score of 3 or 4 on the Modified Medical Research Council Dyspnea Scale (mMRC), i.e. breathlessness after walking 100 yards or after a few minutes on level ground, or when dressing. At the time of the interviews, patients had been receiving mirtazapine for a variable time period of 2 weeks to 5 months. All patients reported an improvement in breathlessness. This was often accompanied by a reduction in anxiety, fewer episodes of panic, as well as improvements in appetite and sleep. Clinical characteristics and reported change in symptoms for all cases are shown in Table 1. Two cases are then described in detail.

Table 1: Clinical Characteristics and reported change in symptoms

Case Number	Age	Sex	Diagnosis	mMRC Dyspnea Scale	Australia-modified Karnofsky Performance scale	HADs	Breathlessness	Anxiety/panic	Appetite	Sleep
Case 1	72	Male	Interstitial Lung Disease (ILD)	4	60	7	+	+	+	
Case 2	68	Male	Chronic Obstructive Pulmonary Disease	4	60	27	+++	+++	++	++
Case 3	70	Female	Interstitial Lung Disease	3	80	8	+		+	
Case 4	64	Male	Chronic Obstructive Pulmonary Disease				+++	+++		
Case 5	74	Female	Chronic Obstructive Pulmonary Disease				++	++	+	+
Case 6	81	Male	Chronic Obstructive Pulmonary Disease				+	+		+

**Case 1:**

Case 1 is a 72 year old male who lives at home with his wife. He was diagnosed with interstitial lung disease 4 years ago, and has a past medical history of bronchiectasis, congestive heart failure and a permanent pacemaker. Prescribed medications at the time of interview included low dose modified release morphine prescribed for chronic breathlessness (5mg twice daily), spironolactone and furosemide. Renal function and liver function tests were within normal limits. His FEV1/FVC ratio was 1.01. Case 1 described experiencing breathlessness on minimal exertion, and whilst speaking in conversation. He found he often had to stop when he became breathless to recover. At baseline Case 1 scored 4 on the mMRC Dyspnea Scale and 60 on the Australia-Modified Karnofsky Performance Scale (AKPS). His 'at worst' breathlessness score on the numerical rating scale was 8, and he scored 7 on the Hospital Anxiety and Depression Scale (HADS). Case 1 was prescribed mirtazapine and was reviewed 2 weeks later. He reported improved breathing and being able to do more including walking further. He described feeling more in control and being able to recover from episodes of breathlessness more quickly. He also noticed an improvement in his appetite. He did not report any adverse effects.

**Case 2:**

Case 2 is a 68 year old male who lives alone. He was diagnosed with severe COPD with emphysema 2 years ago, and is a current smoker. He has a past medical history of hypercapnic respiratory failure for which he uses home non-invasive ventilation, chronic heart failure and benign asbestos plaques. Prescribed medications at the time of assessment included Seretide, Salbutamol, Tiotropium, Spironolactone and Furosemide. Renal function and liver function tests were within normal limits. His FEV1/FVC ratio was 0.35. Case 2 reported severe breathlessness with episodes of panic causing him to regularly attend his local Accident & Emergency department. He described feeling frightened to get out of bed in the morning for fear of triggering breathlessness, and said he didn't often leave the house. At baseline he scored 4 on the mMRC Dyspnea Scale and 60 on the Australia-Modified Karnofsky Performance Scale (AKPS). His 'at worst' breathlessness score on the numerical rating scale was 8, and he scored 27 on the Hospital Anxiety and Depression Scale. Case 2 was prescribed mirtazapine and was reviewed 5 months later. He described feeling less breathless and being able to walk further. He also described sleeping better which he felt impacted positively on his breathing. Case 2 reported no presentations to hospital with breathlessness. He reported no adverse effects but an increased appetite.

## **Discussion/ Conclusion**

This case series is the first to report the use of mirtazapine in the management of chronic breathlessness. Patients with advanced lung disease (COPD and ILD) and chronic breathlessness report mirtazapine to be of benefit to them.

All patients reported an improvement in breathlessness. This was often accompanied by a reduction in anxiety, fewer episodes of panic, as well as improvements in appetite and sleep (as shown in Table 1). No adverse effects were reported despite patients taking mirtazapine for up to 5 months. Given the safety concerns associated with long-term use of other pharmacological treatments in breathlessness such as opioids, data on mirtazapine use for up to 5 months is helpful and contributes towards ongoing pharmacovigilance.

To determine the effectiveness of mirtazapine in alleviating breathlessness and improving quality of life in chronic lung disease, blinded randomised trials are warranted. On the basis of this case series, it looks as if 'improved breathing' and 'being able to do more' are important outcomes. Sleep, appetite, feeling less frightened and being more in control may also be important. Future work should aim to unpick how these domains relate and provide a better understanding of the mechanism of effect of mirtazapine in chronic breathlessness.

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**Conflict of Interest statement:**

The authors declare that they have no conflict of interest

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