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Journal club

Is it safe to prescribe benzodiazepines or opioids for dyspnoea in interstitial lung disease?

Commentary on:

Bajwah S, *et al*. Safety of benzodiazepines and opioids in interstitial lung disease: a national prospective study. *Eur Respir J* 2018; 52: 1801278.

Context

Interstitial lung disease (ILD) encompasses a wide range of pulmonary fibrotic diseases. Idiopathic pulmonary fibrosis (IPF) is the most common form of ILD with an incidence range of 3–9 cases per 100 000 per year for Europe and North America, with most studies showing an increase in incidence over time [1]. Dyspnoea, which is defined by the American Thoracic Society as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity", is a common and debilitating symptom for patients with ILD [2, 3]. However, there is some reluctance to prescribe opiates or benzodiazepines for patients with advanced lung disease due to concern about adverse respiratory effects [4]. To date, there have been few studies investigating the safety of benzodiazepine and opiate use among patients with ILD. Bajwah *et al.* [5] therefore sought to investigate the association between benzodiazepines and opioids on the risk of hospital admission and death in patients with respiratory failure secondary to ILD.

Methods

This was a prospective, longitudinal cohort study of patients aged ≥45 years with fibrotic ILD. Participants were identified as those starting on long-term oxygen therapy (LTOT) between October 2005 and December 2014, who were registered in the Swedish National Registry of Respiratory Failure (Swedevox).

Patients were classified as either exposed or not exposed to opioids or benzodiazepines during the 91 days before admission to the database. Low-dose opioid exposure was defined as ≤30 mg oral morphine equivalents per day. Low-dose benzodiazepine treatment was defined as ≤15 mg oral oxazepam equivalents per day. Bajwah *et al.* [5] analysed the effects of opioid and benzodiazepine treatment on hospital admission and mortality using Fine–Gray and Cox regression with adjustment for potential confounders including age, sex, lung function, blood gases, comorbidities, World Health Organization (WHO) performance status and concurrent medication.

Results

In this population-based, longitudinal cohort study, 1603 patients with fibrotic ILD were started on LTOT between October 2005 and December 2014. Opioids were prescribed to 252 (16%) patients, benzodiazepines to 196 (12%),

Cite as: Finney LJ. Is it safe to prescribe benzodiazepines or opioids for dyspnoea in interstitial lung disease? *Breathe* 2019; 15: 137–139.

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and 59 (4%) patients were prescribed both opioids and benzodiazepines. Benzodiazepines and opioids were more likely to be prescribed in patients who were female, had more comorbidities, had a worse WHO performance status and had a history of more hospital admissions.

There was no association between treatment with benzodiazepines (subdistribution hazard ratio (SHR) 1.2, 95% CI 1.00–1.46) or opioids (SHR 1.14, 95% CI 0.96–1.36) and rates of hospital admission. However, there was a dose-dependent relationship between benzodiazepine treatment and mortality. High-dose benzodiazepines were associated increased mortality (SHR 1.46, 95% CI 1.08–1.97), whereas there was no relationship between low-dose benzodiazepine treatment and mortality (SHR 1.13, 95% CI 0.92–1.38). There was no relationship between treatment with either low-dose opioids (SHR 1.18, 95% CI 0.96–1.45) or high-dose opioids (SHR 1.11, 95% CI 0.89–1.39) and increased mortality. However, there was a weak overall association between opioid use and mortality (hazard ratio 1.18, 95% CI 1.01–1.38). A WHO performance status of 3–4 was also associated with an increased risk of mortality (SHR 2.0, 95% CI 1.67–2.38).

Commentary

In this prospective registry study of oxygen-dependent patients with fibrotic ILD, Bajwah *et al.* [5] found no association between benzodiazepine or opioid treatment and hospital admission. There was no association between opioid use and mortality, but the authors did identify an association between high-dose benzodiazepines (>15 mg oxazepam equivalents per day) and increased mortality.

A key feature of this study is it only included patients who were oxygen dependent. These patients represent a subgroup who are more likely to have advanced disease, and be at greater risk of respiratory failure and other complications. Consequently, the absence of harm is reassuring. However, it is unclear whether these results can be generalised to the population of ILD patients who do not require oxygen supplementation. It is also noted that in table 1, the arterial oxygen tension (P_{aO_2}) in patients breathing oxygen was between 5.4 and 5.7 kPa, whereas P_{aO_2} breathing air was higher at 6.5–6.6 kPa. It is unclear if this is an error by the authors.

The total numbers of patients receiving either opioids (252 patients) or benzodiazepines (196 patients) were relatively small and therefore, the authors acknowledge that they cannot exclude an effect that may be clinically significant. It is also worth noting that although the authors found no association with mortality in the subgroup analysis of low- and high-dose opioids, there was a weak overall association with mortality suggesting the study may have been underpowered.

Dyspnoea is the most prevalent symptom among patients with ILD and has a significant impact on quality of life [3, 6]. Dyspnoea usually occurs because of an imbalance between ventilatory demand and capacity [7]. In ILD, impaired pulmonary gas exchange with increased work of breathing, reduced lung compliance and reduced lung volumes leads to a neuromechanical dissociation resulting in dyspnoea [7]. Anxiety and depression is also common in IPF, which may heighten the perception of dyspnoea due to the effect on central processing [8].

Effective management of dyspnoea in this group of patients presents multiple challenges. Firstly, patients with ILD follow a wide range of disease trajectories. IPF in particular often follows an unpredictable course, punctuated with exacerbations that may cause a sudden and irreversible decline in disease status [9]. Early involvement of palliative care using a modern approach based on needs rather than prognosis is likely to be appropriate in this group of patients [10].

Secondly, the management of dyspnoea is complex as the neurophysiology of dyspnoea remains incompletely understood [11]. While the advent of new antifibrotic agents may prevent lung function decline, a multidisciplinary approach to symptom management including nonpharmacological agents, encouraging self-management and providing psychological support is more likely to be effective [7].

Opioids modulate the sensation of breathlessness by decreasing respiratory drive, altering central perception of dyspnoea, reducing anxiety or acting on peripheral opioid receptors in the lung [7], while benzodiazepines predominantly act by reducing anxiety associated with breathlessness [9]. Opioids have been recommended for the treatment of chronic breathlessness, while there remains little evidence for the effectiveness of benzodiazepines in chronic dyspnoea [10, 13]. This study by Bajwah *et al.* [5] appears to support the use of opioids over benzodiazepines in terms of safety profile in the first instance.

Considering the high prevalence of dyspnoea among patients with ILD, in this study of patients with advanced disease, treatment with opioids or benzodiazepines was surprisingly low. In contrast, a small retrospective UK study of patients with ILD in the last year of life found 49% and 18% were treated with opioids or benzodiazepines respectively [3]. Differences may reflect differences in prescribing between Sweden and the UK, and patient selection. However, low levels of prescribing also suggest there may be reluctance among physicians to prescribe opioids and benzodiazepines for symptom relief in ILD.

Implications for practice

This study provides reassuring data about the safety of low-dose benzodiazepines and opioids for symptomatic treatment of breathlessness in

patients with ILD. While this was a small study, the development of worldwide IPF registries will provide important information about treatments, quality of life and disease outcomes, which will inform prescribing in the future.

Low prescribing levels in the study by Bajwah *et al.* [5] suggest some reluctance among physicians to initiate opioids or benzodiazepines to relieve symptoms of breathlessness among this group of patients. A common concern in patients with advanced lung disease is the adverse effects of respiratory depression [4]. There remains a paucity of data about the safety and efficacy of opiates and benzodiazepines in patients with ILD, with most studies performed in patients with advanced chronic obstructive pulmonary disease [13]. It is likely that when prescribing opioids or benzodiazepines to patients with advanced respiratory disease, patient selection and effective monitoring are key, as respiratory depression appears to be more common in patients who are elderly [14] or where there is polypharmacy [15].

This study is an important first step to understanding the risks of opioids and benzodiazepines in patients with ILD, and improving symptom management. However, further studies including randomised controlled trials of pharmacological interventions and qualitative studies of the impact of these interventions are needed to develop a framework for managing the complex symptom of dyspnoea in patients with ILD.

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Conflict of interest

L.J. Finney has nothing to disclose.

References

1. Hutchinson J, McKeever T, Fogarty A. Increasing global mortality from idiopathic pulmonary fibrosis in the twenty-first century. *Ann Am Thorac Soc*; 11: 1176–1185.
2. Parshall MB, Schwartzstein RM, Adams L, *et al*. An Official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012; 185: 435–452.
3. Bajwah S, Higginson IJ, Ross JR, *et al*. Specialist palliative care is more than drugs: a retrospective study of ILD patients. *Lung* 2012; 190: 215–220.
4. Janssen DJ, de Hosson S, bij de Vaate E, *et al*. Attitudes toward opioids for refractory dyspnea in COPD among Dutch chest physicians. *Chron Respir Dis* 2015; 12: 85–92.
5. Bajwah S, Davies JM, Tanash H, *et al*. Safety of benzodiazepines and opioids in interstitial lung disease: a national prospective study. *Eur Respir J* 2018; 52: 1801278.
6. Lee AS, Mira-Avendano I, Ryu JH, *et al*. The burden of idiopathic pulmonary fibrosis: An unmet public health need. *Respir Med* 2014; 108: 955–967.
7. Mahler DA. Opioids for refractory dyspnea. *Expert Rev Respir Med* 2013; 7: 123–135.
8. Lee YJ, Choi SM, Lee YJ, *et al*. Clinical impact of depression and anxiety in patients with idiopathic pulmonary fibrosis. *PLoS One* 2017; 12: e0184300.
9. Collard HR, Ryerson CJ, Corte TJ, *et al*. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. *Am J Respir Crit Care Med* 2016; 194: 265–275.
10. Maddocks M, Lovell N, Booth S, *et al*. Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. *Lancet* 2017; 390: 988–1002.
11. Spathis A, Booth S, Moffat C, *et al*. The Breathing, Thinking, Functioning clinical model: a proposal to facilitate evidence-based breathlessness management in chronic respiratory disease. *NPJ Prim Care Respir Med* 2017; 27: 27.
12. Simon ST, Higginson IJ, Booth S, *et al*. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev* 2016; 10: CD007354.
13. Ekström M, Nilsson F, Abernethy AA, *et al*. Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review. *Ann Am Thorac Soc* 2015; 12: 1079–1092.
14. Vozoris NT, Wang X, Fischer HD, *et al*. Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J* 2016; 48: 683–693.
15. Krashin D, Murinova N, Jumelle P, *et al*. Opioid risk assessment in palliative medicine. *Expert Opin Drug Saf* 2015; 14: 1023–1033.