Dispneea cronică refractară și utilizarea opioidelor/anxioliticelor în PID (Pneumopatii interstițiale difuze – Fibroza pulmonară idiopatică FPI, fibroze rapide progresive, etc.)

Conf. Dr. Ruxandra Râjnoveanu

UMF “Iuliu Haţieganu” Cluj-Napoca, Disciplina Medicină Paliativă

Sp. Clinic de Pneumoftiziologie “Leon Daniello” Cluj-Napoca

Chronic breathlessness

Experienced by **almost all patients** with **advanced fibrotic ILD**.

One of the most common, burdensome and neglected symptom affecting patients, representing a **major clinical management challenge.**

It has a **devastating impact on patients' lives,** severely limiting their wellbeing and quality of life, and that of their **family, friends and caregivers.**

It results in **high health, social and informal care costs.**

One of the most frequent **causes of emergency hospital admission and attendance.**

Johnson MJ, Yorke J, Hansen-Flaschen J, et al. Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. Eur Respir J 2017; 49: 1602277; Carvajalino S, Reigada C, Johnson MJ, et al. Symptom prevalence of patients with fibrotic interstitial lung disease: a systematic literature review. BMC Pulm Med 2018; 18: 78.; 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

The mechanism behind dyspnea has not yet been fully clarified but is thought to be caused by a **combination of peripheral as well as central nervous mechanisms.**

It has been proved that **different combinations of afferent inputs lead to different sensations** .

Kohberg C, Andersen CU, Bendstrup E. Opioids: an unexplored option for treatment of dyspnea in IPF. European clinical respiratory journal. 2016 Jan 1;3(1):30629.

Clinically Important Differences in the Intensity of Chronic Refractory Breathlessness

- There is consensus that the **0-100 mm visual analogue scale (VAS),**

0-10 numerical rating scale (NRS), and **modified Borg scale** are appropriate unidimensional measures of chronic breathlessness intensity.

- **MCID**, different from a statistically significant difference, is defined as **the change in a breathlessness intensity score discernible to a patient as indicative of improvement or deterioration.**

- Dorman S, Jolley C, Abernethy A, et al. Researching breathlessness in palliative care: consensus statement of the National Cancer Research Institute Palliative Care Breathlessness Subgroup. Palliat Med 2009;23:213e227.
- Oxberry SG, Bland JM, Clark AL, Cleland JG, Johnson MJ. Minimally clinically important difference (MCID) in chronic breathlessness: every little helps. Am Heart J 2012;164:229e235.
- Johnson MJ, Bland JM, Oxberry SG, Abernethy AP, Currow DC. Clinically important differences in the intensity of chronic refractory breathlessness. Journal of pain and symptom management. 2013 Dec 1;46(6):957-63.

Clinically Important Differences in the Intensity of Chronic Refractory Breathlessness

- There is a distinction between a clinically detectable change and a clinically important difference.

- **The consensus statement recommends that a clinically important difference for chronic refractory breathlessness scores is 1 point on an NRS scale or 10 mm on a VAS scale.**

- **This level of improvement should be the therapeutic target.**

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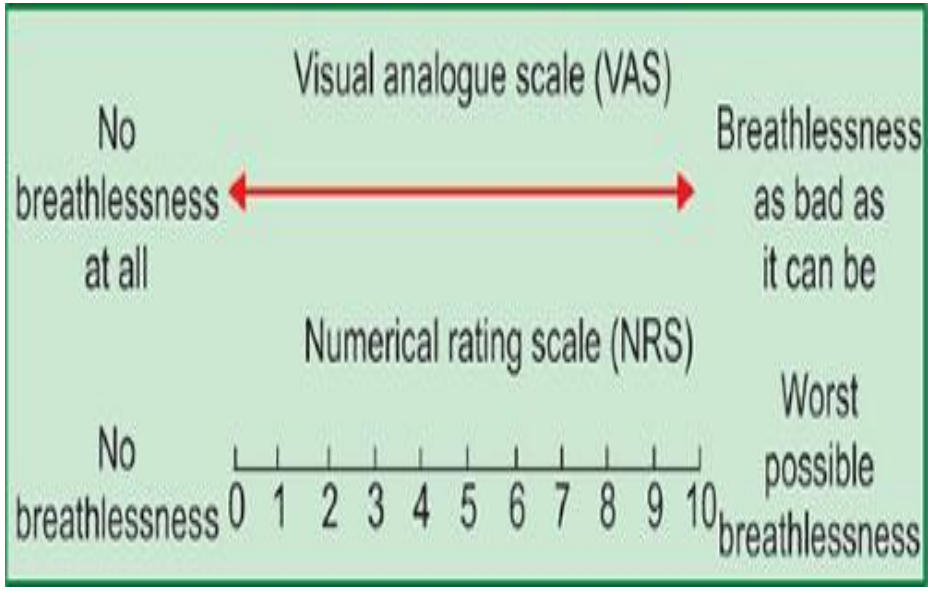

- Booth S. Improving research methodology in breathlessness: a meeting convened by the MRC Clinical Trials Unit and the Cicely Saunders Foundation. Palliative Medicine. 2006 Apr;20(3):219-20.
- Johnson MJ, Bland JM, Oxberry SG, Abernethy AP, Currow DC. Clinically important differences in the intensity of chronic refractory breathlessness. Journal of pain and symptom management. 2013 Dec 1;46(6):957-63.

The management of IPF

Dyspnea in IPF results from both respiratory and circulatory limitations: reduced lung compliance, loss of lung volume, increased dead space ventilation, increased respiratory drive, gas exchange abnormalities and pulmonary hypertension.

In turn, **breathlessness treatment is a multifaceted process** involving effective treatment of comorbidities, rehabilitation, pharmacological and oxygen treatment and non-invasive ventilation.

Plantier L, Cazes A, Dinh-Xuan A-T, Bancal C, Marchand-Adam S, Crestani B. Physiology of the lung in idiopathic pulmonary fibrosis. *Eur Respir Rev*. (2018) 27:170062. doi: 10.1183/16000617.0062-2017

The management of IPF

Requires **collaboration among members of the healthcare team, family members, and caregivers**

to **provide patient education and support,**

as well as **management of symptoms, comorbidities, and palliative care**.

Pleasants R, Tighe RM. Management of idiopathic pulmonary fibrosis. Ann Pharmacother 2019;53:1238–48. doi: 10.1177/1060028019862497

Lečić SK, Javorac J, Živanović D, Lovrenski A, Tegeltija D, Svorcan JZ, Maksimović J. Management of musculoskeletal pain in patients with idiopathic pulmonary fibrosis: a review. Upsala Journal of Medical Sciences. 2022;127.

- Although the **current IPF guidelines**

recommend symptom-based approach and palliative care

as an adjunct to disease-focused care,

most patients with IPF do not receive optimal palliative care

throughout the course of the disease or even at the end of life.

- Lindell KO, Liang Z, Hoffman LA, et al. Palliative care and location of death in decedents with idiopathic pulmonary fibrosis. Chest 2015;147:423e429.
- Ahmadi Z, Wysham NG, Lundstrom S, et al. End-of-life care in oxygen-dependent ILD compared with lung cancer: a national population-based study. Thorax 2016;71:510e516.
- Akiyama N, Fujisawa T, Morita T, Mori K, Yasui H, Hozumi H, Suzuki Y, Karayama M, Furuhashi K, Enomoto N, Nakamura Y. Palliative care for idiopathic pulmonary fibrosis patients: pulmonary physicians' view. Journal of Pain and Symptom Management. 2020 Nov 1;60(5):933-40.

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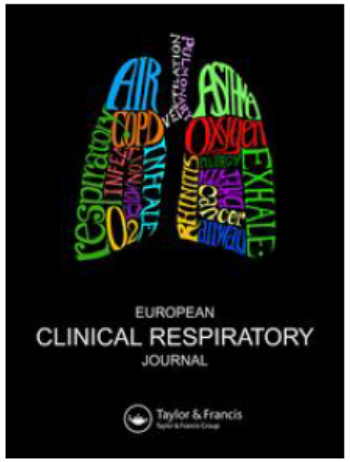
BRIEF REPORT Open Access

Patients with Terminal Interstitial Pneumonia Require Comparable or More Palliative Pharmacotherapy for Refractory Dyspnea than Patients with Terminal Lung Cancer

Hiroko Okabayashi, MD,[1,2,*,**] Hideya Kitamura, PhD,[1] Satoshi Ikeda, PhD,[1] Akimasa Sekine, PhD,[1] Tsuneyuki Oda, PhD,[1] Tomohisa Baba, MD,[1] Eri Hagiwara, PhD,[1] Takuro Sakagami, PhD,[2] and Takashi Ogura, MD[1]

ILD patients had a significantly longer period of breathlessness and lower rates of complete relief from breathlessness than LC patients.

Okabayashi H, Kitamura H, Ikeda S, Sekine A, Oda T, Baba T, Hagiwara E, Sakagami T, Ogura T. Patients with Terminal Interstitial Pneumonia Require Comparable or More Palliative Pharmacotherapy for Refractory Dyspnea than Patients with Terminal Lung Cancer. **Palliative Medicine Reports. 2021** Jun 1;2(1):188-93.



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European Clinical Respiratory Journal

ISSN: (Print) 2001-8525 (Online) Journal homepage: https://www.tandfonline.com/loi/zecr20

Opioids: an unexplored option for treatment of dyspnea in IPF

Charlotte Kohberg, Charlotte Uggerhøj Andersen & Elisabeth Bendstrup

Morphine in the treatment of dyspnea has been investigated but with conflicting results.

Only very few high quality randomized, placebo-controlled studies had investigated the effect of opioids in IPF

Kohberg C, Andersen CU, Bendstrup E. Opioids: an unexplored option for treatment of dyspnea in IPF. European clinical respiratory journal. 2016 Jan 1;3(1):30629.
Janowiak P, Szymanowska-Narloch A, Siemińska A. IPF Respiratory Symptoms Management—Current Evidence. Frontiers in Medicine. 2022;9.

- By acting upon their central and peripheral nervous system receptors **opoids can decrease anxiety, modulate central perception of dyspnea and reduce respiratory drive without significant changes in blood gases.**

Janowiak P, Szymanowska-Narloch A, Siemińska A. IPF Respiratory Symptoms Management—Current Evidence. Frontiers in Medicine. 2022;9.

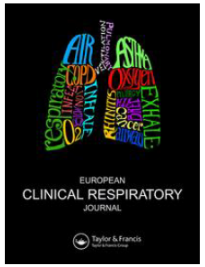
Opioids

- Are the **primary pharmacologic treatment for refractory dyspnea in patients with respiratory diseases**
- Opioids are being implemented variably in practice for chronic breathlessness.
- **There is level 1a evidence to support the use of opioids for breathlessness.**
- **The best evidence is for 10–30 mg daily de novo low-dose oral sustained-release morphine in opioid-naïve patients.**
- **This should be considered the current standard of care** following independent, regulatory scrutiny by one of the world's therapeutics regulatory bodies.

Akiyama N, Fujisawa T, Morita T, Mori K, Yasui H, Hozumi H, Suzuki Y, Karayama M, Furuhashi K, Enomoto N, Nakamura Y. Palliative care for idiopathic pulmonary fibrosis patients: pulmonary physicians' view. Journal of Pain and Symptom Management. 2020 Nov 1;60(5):933-40.

- Results were inconsistent, but in **some studies systemic morphine administration showed a significant improvement in the dyspnea score on a visual analog scale without observation of severe side effects.**

- **Nebulized morphine had no effect on dyspnea**.



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Opioids: an unexplored option for treatment of dyspnea in IPF

Charlotte Kohberg, Charlotte Uggerhøj Andersen & Elisabeth Bendstrup

Beneficial effect of morphine on dyspnea

- The most prominent effect was reported by Allen et al, who found a 50-mm decrease in a dyspnea VAS scale, 15 and 30 min after injection of 2.5/5 mg morphine (5 mg for patients 50 kg) subcutaneously.

- Constipation was reported as an adverse effect to morphine treatment, but **respiratory depression, the most feared side effect, was not observed in any of the studies.**

Allen S, Raut S, Woollard J, Vassallo M. Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. Pall Med. 2005; 19: 12830.
Kohberg C, Andersen CU, Bendstrup E. Opioids: an unexplored option for treatment of dyspnea in IPF. European clinical respiratory journal. 2016 Jan 1;3(1):30629.

Morphine-related adverse events are common but mostly mild and self-limiting on withdrawal of drug.

Early and meticulous management of constipation, nausea and vomiting is needed **particularly in the first week of administration**.

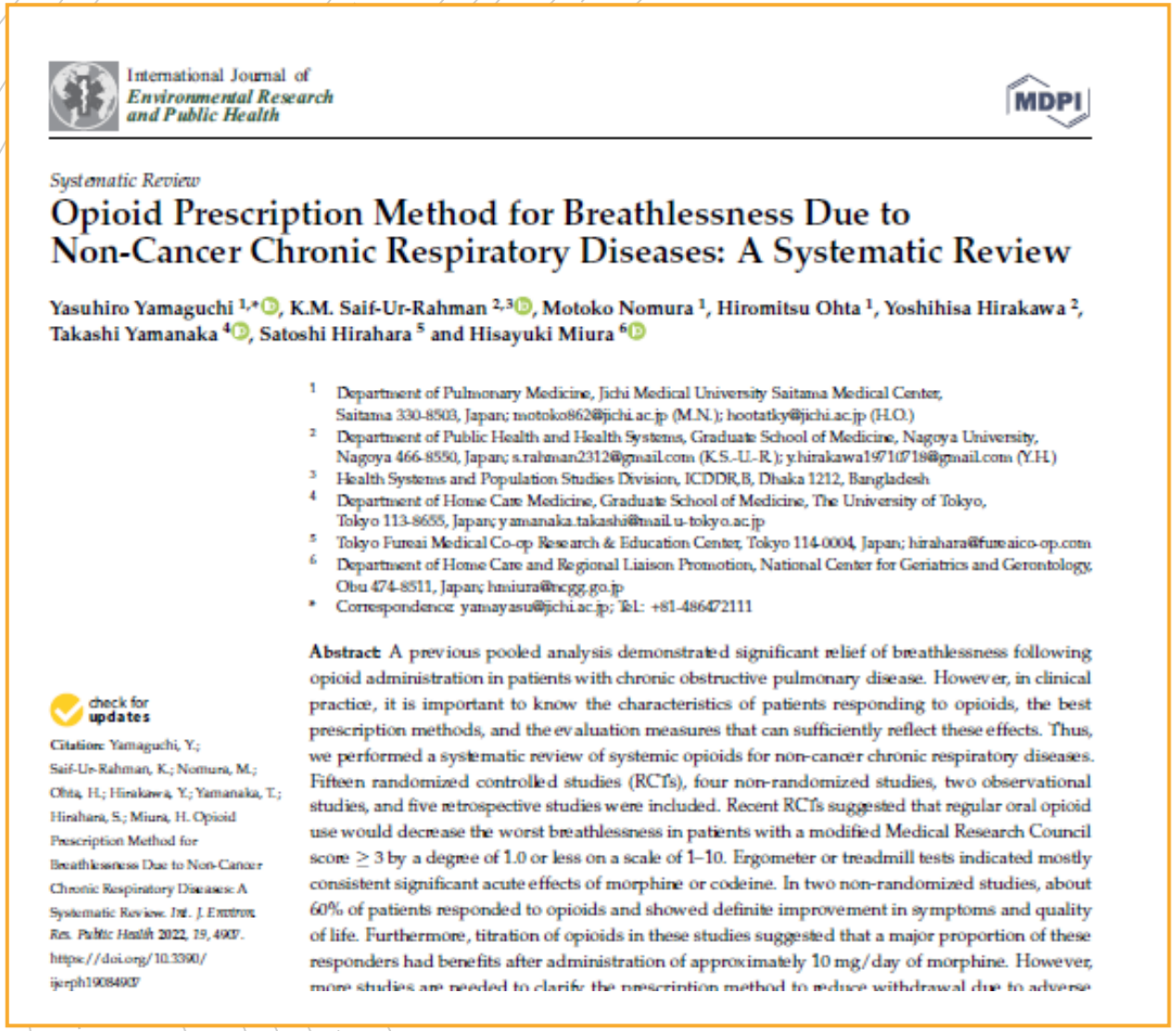
Serious adverse events are no more common than placebo in clinical studies.

Kohberg C, Andersen CU, Bendstrup E. Opioids: an unexplored option for treatment of dyspnea in IPF. European clinical respiratory journal. 2016 Jan 1;3(1):30629.

Patients with combined pulmonary emphysema and fibrosis (CPFE)

- **It can be speculated that this phenotype** and COPD phenotypes such as those with very severe emphysema **will benefit more from opioid treatment than those with a chronic bronchitis phenotype.**

Kohberg C, Andersen CU, Bendstrup E. Opioids: an unexplored option for treatment of dyspnea in IPF. European clinical respiratory journal. 2016 Jan 1;3(1):30629.



International Journal of *Environmental Research and Public Health*

MDPI

Systematic Review

Opioid Prescription Method for Breathlessness Due to Non-Cancer Chronic Respiratory Diseases: A Systematic Review

Yasuhiro Yamaguchi [1,*], K.M. Saif-Ur-Rahman [2,3], Motoko Nomura [1], Hiromitsu Ohta [1], Yoshihisa Hirakawa [2], Takashi Yamanaka [4], Satoshi Hirahara [5] and Hisayuki Miura [6]

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5 Tokyo Fureai Medical Co-op Research & Education Center, Tokyo 114-0004, Japan; hirahara@fureaico-op.com
6 Department of Home Care and Regional Liaison Promotion, National Center for Geriatrics and Gerontology, Obu 474-8511, Japan; hmiura@ncgg.go.jp
* Correspondence: yamayasu@jichi.ac.jp; Tel.: +81-486472111

Abstract: A previous pooled analysis demonstrated significant relief of breathlessness following opioid administration in patients with chronic obstructive pulmonary disease. However, in clinical practice, it is important to know the characteristics of patients responding to opioids, the best prescription methods, and the evaluation measures that can sufficiently reflect these effects. Thus, we performed a systematic review of systemic opioids for non-cancer chronic respiratory diseases. Fifteen randomized controlled studies (RCTs), four non-randomized studies, two observational studies, and five retrospective studies were included. Recent RCTs suggested that regular oral opioid use would decrease the worst breathlessness in patients with a modified Medical Research Council score ≥ 3 by a degree of 1.0 or less on a scale of 1–10. Ergometer or treadmill tests indicated mostly consistent significant acute effects of morphine or codeine. In two non-randomized studies, about 60% of patients responded to opioids and showed definite improvement in symptoms and quality of life. Furthermore, titration of opioids in these studies suggested that a major proportion of these responders had benefits after administration of approximately 10 mg/day of morphine. However, more studies are needed to clarify the prescription method to reduce withdrawal due to adverse

check for updates

Citation: Yamaguchi, Y.; Saif-Ur-Rahman, K.; Nomura, M.; Ohta, H.; Hirakawa, Y.; Yamanaka, T.; Hirahara, S.; Miura, H. Opioid Prescription Method for Breathlessness Due to Non-Cancer Chronic Respiratory Diseases: A Systematic Review. *Int. J. Environ. Res. Public Health* **2022**, *19*, 4907. https://doi.org/10.3390/ijerph19084907

- 15 randomized controlled studies (RCTs),
- 4 non-randomized studies,
- 2 observational studies,
- 5 retrospective studies were included

Int. J. Environ. Res. Public Health **2022**, 19, 4907

- Recent RCTs suggested that **regular oral opioid use would decrease the worst breathlessness** in patients with a **modified Medical Research Council score ≥ 3** by a degree of 1.0 or less on a scale of 1–10.

- In two non-randomized studies, about **60% of patients responded to opioids and showed definite improvement in symptoms and quality of life**.

- Titration of opioids in these studies suggested that a major proportion of these responders had benefits after administration of approximately 10 mg/day of morphine.

Yamaguchi Y, Saif-Ur-Rahman KM, Nomura M, Ohta H, Hirakawa Y, Yamanaka T, Hirahara S, Miura H. Opioid Prescription Method for Breathlessness Due to Non-Cancer Chronic Respiratory Diseases: A Systematic Review. International Journal of Environmental Research and Public Health. 2022 Jan;19(8):4907.

- In clinical practice, physicians and patients experience difficulty in palliating breathlessness when chronic respiratory diseases, such as COPD and **interstitial lung disease (ILD**), advance to breathlessness corresponding to a **modified Medical Research Council (mMRC) score 3 or 4.**

- **The expected efficacy of opioids should be determined for these patients.**

- **Simultaneously, both physicians and patients** with non-cancer diseases **prioritize the prevention of adverse events that can affect daily activities or prognosis.**

- **The safest prescription methods should be pursued in order to break the barriers that prevent the use of opioids for the palliation of breathlessness in non-cancer diseases**.

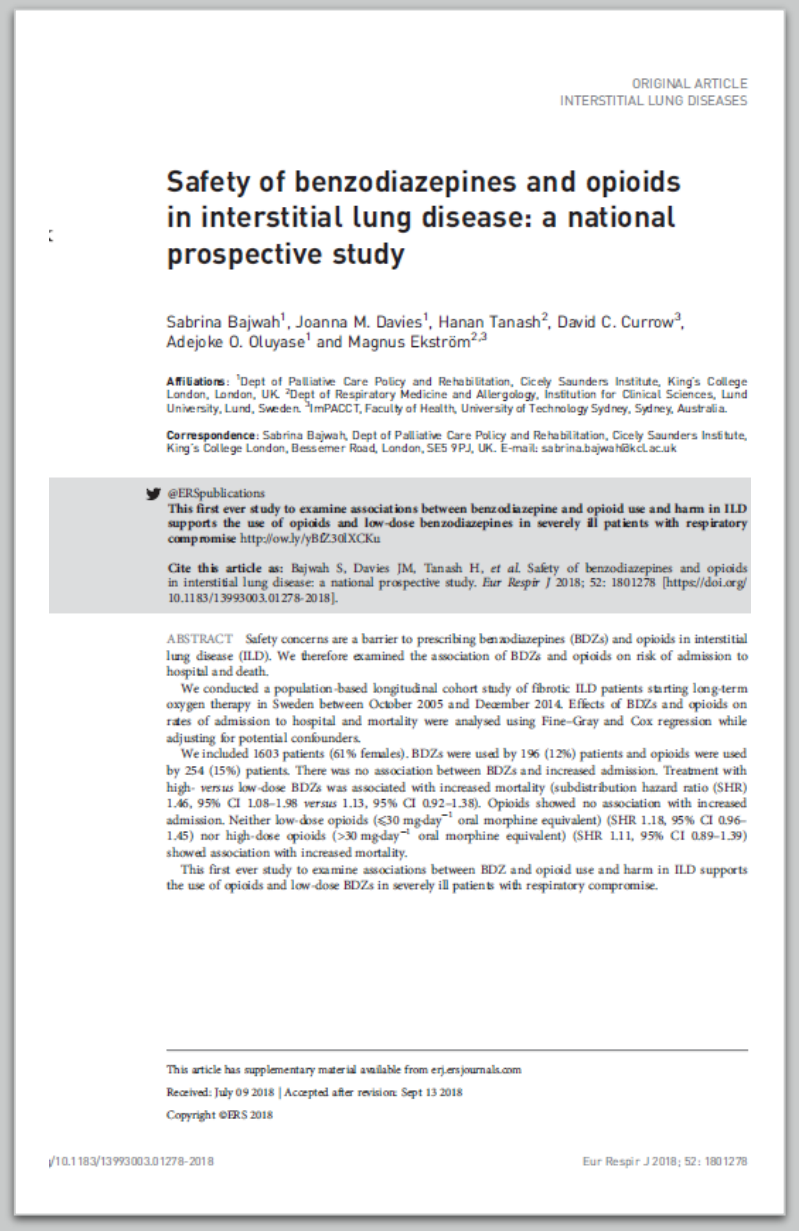
Int. J. Environ. Res. Public Health **2022**, 19, 4907

Attitudes of patients towards opioid treatment for chronic breathlessness are mixed, with 37% of patients willing to use opioids, 25% unwilling and 38% of patients indecisive.

Physicians are an important source of information for these patients.

Pulmonologists experienced greater difficulty in providing palliative care to patients with IPF than to those with lung cancer.

Verberkt CA, van den Beuken-van Everdingen MHJ, Wouters EFM, et al. Attitudes of patients with chronic breathlessness towards treatment with opioids. Eur Respir J 2020; 55: 1901752.
Yamaguchi Y, Saif-Ur-Rahman KM, Nomura M, Ohta H, Hirakawa Y, Yamanaka T, Hirahara S, Miura H. Opioid Prescription Method for Breathlessness Due to Non-Cancer Chronic Respiratory Diseases: A Systematic Review. International Journal of Environmental Research and Public Health. 2022 Jan;19(8):4907.



ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASES

Safety of benzodiazepines and opioids in interstitial lung disease: a national prospective study

Sabrina Bajwah[1], Joanna M. Davies[1], Hanan Tanash[2], David C. Currow[3], Adejoke O. Oluyase[1] and Magnus Ekström[2,3]

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@ERSpublications
This first ever study to examine associations between benzodiazepine and opioid use and harm in ILD supports the use of opioids and low-dose benzodiazepines in severely ill patients with respiratory compromise http://ow.ly/yBfZ30lXCKu

Cite this article as: 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 [https://doi.org/10.1183/13993003.01278-2018].

ABSTRACT Safety concerns are a barrier to prescribing benzodiazepines (BDZs) and opioids in interstitial lung disease (ILD). We therefore examined the association of BDZs and opioids on risk of admission to hospital and death.

We conducted a population-based longitudinal cohort study of fibrotic ILD patients starting long-term oxygen therapy in Sweden between October 2005 and December 2014. Effects of BDZs and opioids on rates of admission to hospital and mortality were analysed using Fine–Gray and Cox regression while adjusting for potential confounders.

We included 1603 patients (61% females). BDZs were used by 196 (12%) patients and opioids were used by 254 (15%) patients. There was no association between BDZs and increased admission. Treatment with high- *versus* low-dose BDZs was associated with increased mortality (subdistribution hazard ratio (SHR) 1.46, 95% CI 1.08–1.98 *versus* 1.13, 95% CI 0.92–1.38). Opioids showed no association with increased admission. Neither low-dose opioids (≤30 mg·day^{-1} oral morphine equivalent) (SHR 1.18, 95% CI 0.96–1.45) nor high-dose opioids (>30 mg·day^{-1} oral morphine equivalent) (SHR 1.11, 95% CI 0.89–1.39) showed association with increased mortality.

This first ever study to examine associations between BDZ and opioid use and harm in ILD supports the use of opioids and low-dose BDZs in severely ill patients with respiratory compromise.

This article has supplementary material available from erj.ersjournals.com

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- Population-based longitudinal cohort study of included physician-diagnosed pulmonary fibrotic ILD patients starting long-term oxygen therapy in Sweden between October 2005 and December 2014.
- Causes of pulmonary fibrosis included (but were not limited to) IPF and nonspecific interstitial pneumonia.
- This first ever study to examine associations between benzodiazepine and opioid use and harm in ILD.
- **It supports the use of opioids and low-dose benzodiazepines in severely ill patients with respiratory compromise.**

- 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

- **Opioids showed no association with increased admission.**

- **Neither low-dose opioids (⩽30 mg·day−1 oral morphine equivalent) nor high-dose opioids (>30 mg·day−1 oral morphine equivalent) showed association with increased mortality.**

- There was no association between BDZs and increased admission.

- Treatment with high- versus low-dose BDZs (⩽15 mg·day−1 oral oxazepam equivalent) was associated with increased mortality.

- 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

Terminal-stage interstitial pneumonia

The **efficacy of sustained-release morphine or diamorphine in patients with refractory dyspnea and predicted prognosis of one month or more** were reported in the study on respiratory diseases including ILD.

In a study that evaluated **the safety of sustained-release opioids in ILD with LTOT, opioids were not associated with increased hospital admissions or mortality.**

Three reports describe the **efficacy and safety of continuous morphine administration in terminally ill IP patients**.

Allen S, Raut S, Woollard J, Vassallo M: Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. Palliat Med 2005;

19:128–130. 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. Takeyasu M, Miyamoto A, Kato D, et al.: Continuous intravenous morphine

infusion for severe dyspnea in terminally ill insterstitial pneumonia patients. Intern Med 2016;55:725–729. Matsuda Y, Maeda I, Tachibana K, et al.: Low-dose morphine dyspnea in terminally ill patients with idiopathic interstitial pneumonias. J Palliat Med 2017;20:879–883.

Terminal-stage interstitial pneumonia

- The efficacy of continuous morphine administration for terminal dyspnea in IP patients was similar to that in LC patients for a short time after initiation,

- But just before death, **more patients in the IP group required concomitant use of midazolam and morphine.**

- **Palliative sedation** is a therapeutic option in cases wherein symptom relief is difficult to achieve.

- Midazolam has been mentioned as the first-choice drug for palliative sedation in several guidelines

Hiroko Okabayashi et al., Palliative Medicine Reports, Volume 2.1, 2021
DOI: 10.1089/pmr.2021.0010

Conclusions

- Chronic refractory dyspnea is common in almost all advanced ILD patients.
- 10-30 mg·day−1 oral morphine equivalent is the current evidence-based dose range for opioid treatment for chronic breathlessness.
- Morphine-related adverse events are common but mostly mild.
- Low dose opioids are effective and safe in the palliative management of IPF including frail elderly patients, terminal-stages or with LTOT.