Pain in patients with chronic obstructive pulmonary disease indicated for post-acute pulmonary rehabilitation

Eléonore F van Dam van Isselt¹,², Karin H Groenewegen-Sipkema³, Monica van Eijk¹, Niels H Chavannes¹ and Wilco P Achterberg¹

Abstract
Pain is a significant problem in stable chronic obstructive pulmonary disease (COPD) and is associated with other symptoms, worse health status and lower functional status. Not much is known about pain in unstable disease. The primary aim of the present study is to investigate prevalence, characteristics and relationships of pain in patients with COPD hospitalized for an acute exacerbation (AECOPD) and indicated for post-acute pulmonary rehabilitation (PR). This cross-sectional observational study included 149 patients (mean age 70.8 (± 7.9) years, 49% male, mean forced expiratory volume in one second as percentage of predicted value 35.3 (± 12.6)). Pain was assessed using the brief pain inventory. Functional status and health status were measured using the six-minute walking test (6MWT), the Barthel index (BI) and the clinical COPD questionnaire (CCQ), respectively. Pain was prevalent in 39.6% of all patients. Symptom burden was high, especially in patients with pain. Although we found no difference in objective measurements of functional status (6MWT, BI), patients with pain had clinically relevant lower health status (CCQ), attributed to the functional domain. Pain in patients hospitalized for AECOPD and indicated for post-acute PR is a relevant problem and needs more attention. Incorporation of standard pain assessment during exacerbations and post-acute PR is recommended.

Keywords
Pain, unstable COPD, brief pain inventory, symptom burden, health status

Date received: 22 May 2018; accepted: 18 September 2018

Background
Pain is a clinically relevant symptom in chronic obstructive pulmonary disease (COPD) with prevalences ranging from 32% to 85%, depending on setting, sample and measurements used.¹,² Pain is negatively associated with health-related quality of life (HRQoL).¹⁻⁵ Many symptoms are associated with pain, of which dyspnoea, anxiety, depression and insomnia are the most frequent.¹ Furthermore, these symptoms cluster and aggravate each other. Lohne et al. first described this process of multiple concurrent symptoms reinforcing each other and called it the ‘vicious COPD circle’.⁶ In this concept, derived from

¹ Department of Public Health and Primary Care, Leiden University Medical Centre, Leiden, The Netherlands
² Zorggroep Solis, Deventer, The Netherlands
³ Pulmonary Department, Deventer Hospital, Deventer, The Netherlands

Corresponding author:
Eléonore F van Dam van Isselt, Department of Public Health and Primary Care, Leiden University Medical Centre, PO box 9600, 2300 RC Leiden, The Netherlands.
Email: e.f.vandamvanisselt@lumc.nl
a qualitative study on pain in patients with severe COPD, pain was described as ‘tying up the body’, which made breathing difficult, leading to breathlessness and more pain. Pain also induced anxiety, depression and insomnia, causing more pain and psychological problems.6 Recently, Lee et al. reported similar results on the negative interaction between several symptoms and pain.7

Pain in COPD is also associated with diminished physical activity and lower functional exercise capacity,8,9 often worsened by pain-related fear of movement.4,7 The relationship between pain, symptoms and physical activity is important, since lifelong adherence to physical activity is essential to improve HRQoL and prognosis in COPD.

Acute exacerbations in COPD (AECOPD) play a key role. They represent a major burden for individual patients,10 are the most frequent reason for hospital admissions and deaths among patients with COPD11 and negatively influence HRQoL and functional capacity,10,11 often leading to rehospitalizations, further decline of health status and high mortality rates.12,13 The prevalence of pain and its relationship with other symptoms, functional capacity and HRQoL in unstable disease is however unknown, as data on pain during AECOPD are lacking.1,2 Hypothetically, pain in patients with AECOPD might be aggravated compared to the stable state due to the mentioned vicious circle of symptoms, since acute exacerbations are defined as an increase in symptoms such as dyspnoea and cough. Post-acute pulmonary rehabilitation (PR) is an effective and safe intervention to counteract the adverse effects of hospital admission for AECOPD on symptom burden and physical functioning.10 From this viewpoint, post-acute PR could be an effective non-pharmacological intervention to reduce pain in unstable COPD, as it might counteract the pain-related vicious circles in COPD.14 Also, as pain management is preferably undertaken using multi-domain strategies (e.g. psychological, physical, behavioural and pharmacological9), it might be a separate goal in post-acute PR by means of improving muscle strength, exercise capacity and coping. On the other hand, pain might negatively influence outcomes of post-acute PR in terms of HRQoL and functional status. However, as far as we know, no studies on the role of pain in post-acute PR are available in literature.

Recently, Harrison et al.14 did report on the role of pain in PR and concluded that a pain intervention, as part of a PR education programme, seems warranted, as high pain prevalence and intensity, in combination with under-diagnosis and undertreatment, might negatively influence adherence to and outcomes of PR. Furthermore, as PR can aggravate pain in the short term, education of healthcare professionals and patients is important to optimize adherence to PR.14

In summary, pain is a relevant problem in patients with COPD, with relationships to several symptoms and diminished physical activity, causing several pain-related vicious circles. Furthermore, pain might negatively influence adherence to and outcomes of PR. However, literature on pain in unstable COPD and in relation to post-acute PR is lacking. Therefore, the primary aim of the present study is to investigate prevalence and characteristics of pain in patients with COPD hospitalized for an acute exacerbation and indicated for post-acute PR. Secondary aim is to investigate the relationship between pain, other symptoms, functional status and health status.

Methods

Study design

This cross-sectional observational study is part of a larger real-life prospective cohort study, conducted in the pulmonary department of two local hospitals to investigate the effects of a post-acute PR programme on patients with COPD. Data collected during the hospital stay (the start of the study) were used. The Medical Ethics Committee of Leiden University Medical Centre approved the study (P14.248) and the study design was registered in the Netherlands National Trial Register (NTR6261).

Participants

Patients were eligible when diagnosed with COPD and hospitalized with an acute exacerbation and indicated for post-acute PR based on standard criteria (Box 1). All participants signed a written informed consent. Patients were included in the study from January 2015 through December 2017.
Measurements

The following patient and disease characteristics were accessed from the patient’s file: age, sex, spirometry (according to the Global Initiative for Chronic Obstructive Disease (GOLD) guidelines\(^1\)\(^5\)), co-morbidity (Charlson co-morbidity index (CCI))\(^1\)\(^6\) and smoking status (yes/no). Nutritional status was measured by calculating body mass index (BMI; kg/m\(^2\)) and assessing the fat-free mass index (FFMI; kg/m\(^2\)) by electrical bio-impedance. Impaired nutritional status was defined as FFMI <16 (men) or <15 (women) kg/m\(^2\), or in case of missing FFMI data, BMI <21 kg/m\(^2\)\(^1\)\(^7\).

Pain

Pain was measured using the Dutch version of the brief pain inventory (BPI).\(^1\)\(^8\) The BPI is a valid, reliable, comprehensive and widely used pain questionnaire in COPD studies and clinical practice.\(^1\)\(^9\) First, patients are asked to indicate whether they are generally bothered by pain in the past week (yes/no), and if so, they then completed the full BPI, which consists of nine items subdivided into three components; (i) pain location using the body outline diagram on which patients can mark the location(s) of their pain, (ii) pain intensity which consists of four items that ask about pain intensity ‘now’, ‘worst level’, ‘least level’ and ‘on average’ using a numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain) and (iii) pain interference with seven items evaluating how pain interferes with seven activities of daily life using a NRS ranging from 0 (no interference) to 10 (complete interference). In addition, two items address pain treatment and pain relief by treatment, ranging from 0% (no relief) to 100% (complete relief).

Pharmaceutical pain treatment was also assessed using the medical charts of all patients. Categories were based on the pain ladder of the World Health Organization\(^2\)\(^0\); (1) non-opioid, (2) weak opioid and (3) strong opioid. All prescriptions were coded as ‘daily use’ and/or ‘as needed’.

Symptom burden

In addition to pain, the following symptoms were measured: Dyspnoea was measured using the modified Medical Research Council (mMRC) dyspnoea scale (scores range from 0 to 4); moderate to severe dyspnoea was defined as having a score of ≥2\(^1\)\(^5\); fatigue, insomnia, muscle weakness and anorexia were measured using a NRS (scale 0–100) and were considered to be moderate to severe with a score of ≥40.\(^2\)\(^1\)\(^,2\)\(^2\) Symptoms of anxiety and depression were measured using the hospital anxiety and depression scale (HADS). A score of >7 points on either subscale indicates moderate to severe symptoms of anxiety or depression.\(^2\)\(^3\)

Functional status

Activities of daily living (ADL) were measured using the Barthel index (BI).\(^2\)\(^4\) The BI is a valid and reliable instrument to assess ADL. Total score ranges from 0 to 20, with 20 representing complete functional independence, 15–19 mild-, 10–14 moderate- and <10 severe care dependency, respectively.\(^2\)\(^5\) Exercise capacity was measured with the six-minute walking test (6MWT), according to ERS guidelines. The 6MWT is a reliable, practical and widely used instrument to measure exercise capacity in patients with COPD.\(^2\)\(^6\)

Disease-specific health status

Disease-specific health status was measured using the clinical COPD questionnaire (CCQ).\(^2\)\(^7\) The CCQ is a
validated and reliable 10-item self-administered questionnaire with three subdomains; symptoms, function and mental status. Items are scored on a Likert-type scale ranging from 0 to 6. The final score is the sum of all items divided by 10 and a score of >2.0 indicates impaired health status. The minimal clinical important difference of the CCQ total score is +0.4.28

Statistical analysis
All data were processed using the SPSS (IBM SPSS Statistics for Windows version 23.0). Categorical variables are described as frequencies, while continuous variables were tested for normality and are presented as mean and standard deviation (SD) or median and interquartile range (IQR) in case of skewed data. Differences between patients with and without pain were tested with independent sample t-test or χ² test where appropriate. In case of skewed data, non-parametric tests were used. Statistical significance was defined as a p value <0.05 (two-sided level of significance).

Results
General results
In total, 158 patients participated in the original study. Of these, nine patients (5.7%) had not completed the BPI and were excluded from the current analyses. Hence, the data of 149 patients (mean age 70.8 (± 7.9) years, 49% male, mean forced expiratory volume in one second as percentage of predicted value (FEV₁%, predicted) 35.3 (± 12.6)) were analysed (Table 1). Pain was prevalent in 59 patients (39.6%). No differences in demographic data (age, sex) and disease characteristics (FEV₁, FEV₁% predicted, co-morbidity score, nutritional status, smoking status) were found between patients with and without pain. Considering the functional status, results of the BI showed only mild care dependency (BI: 18 (15–20)), but exercise capacity was considerably limited (6MWT: 200.3 (110.8)). No differences in functional status were found between the two groups (p = 0.34; p = 0.42, respectively).

Characteristics of pain and pain treatment
In total, 94 marks were placed on the body outline diagram by 44 patients. In 15 patients with pain, the body outline diagram was blank. Pain was most frequently located in the trunk region (Figure 1). More than half (57%) of the patients with pain indicated two or more locations of pain on the body outline diagram. Mean pain intensity scores on the BPI ranged from 2.7 (± 2.3) (least pain) to 6.4 (± 2.5) (worst pain). ‘Average pain’ and ‘pain right now’ showed mean scores of 4.3 (± 2.3) and 4.1 (± 3.1), respectively. Interference domain scores were highest for interference with normal work (5.9 (± 3.3)), walking ability (5.6 (3.1)) and general activity (5.5 (3.0)). Patients

Table 1. Characteristics of the study population.a

|                           | Total group (N = 149) | Patients with pain (N = 59) | Patients without pain (N = 90) | p Value |
|---------------------------|-----------------------|----------------------------|-------------------------------|--------|
| Maleb                     | 73 (49)               | 25 (42.4)                  | 48 (53.3)                     | 0.24   |
| Age in yearsc             | 70.8 (7.9)            | 69.5 (7.3)                 | 71.7 (8.2)                    | 0.08   |
| FEV₁ (L)                  | 0.88 (0.35)           | 0.92 (0.37)                | 0.86 (0.33)                   | 0.28   |
| FEV₁% predictedc          | 35.3 (12.6)           | 37.3 (12.6)                | 33.9 (12.5)                   | 0.11   |
| Smokingb                  | 45 (30.2)             | 19 (32.2)                  | 26 (28.9)                     | 0.72   |
| CCI d i                   | 2 (1–3)               | 2 (1–3)                    | 2 (1–3)                       | 0.75   |
| BMIc                      | 24.8 (5.4)            | 25.3 (6.1)                 | 24.5 (4.9)                    | 0.33   |
| FFMIc                      | 16.2 (2.6)            | 16.4 (2.7)                 | 16.1 (2.5)                    | 0.63   |
| Impaired nutritional statusb | 52 (34.9)            | 21 (35.6)                  | 31 (34.4)                     | 0.89   |
| BI d                      | 18 (15–20)            | 18 (16–20)                 | 18 (15–20)                    | 0.34   |
| 6MWTc                     | 200.3 (110.8)         | 212.0 (111.5)              | 201.9 (114.4)                 | 0.42   |

FEV₁% predicted: forced expiratory volume in one second as percentage of predicted value; CCI: Charlson comorbidity index; BMI: body mass index; FFMI: fat-free mass index; BI: Barthel index; 6MWT: six-minute walking test; SD: standard deviation; IQR: interquartile range.

aLevel of significance: p < 0.05.
bCounts with percentage are indicated.
cMean values (SD).
dMedian (IQR).
experienced the least interference with mood (3.6 (± 2.9)) and relations with others (3.3 (± 2.9)).

Patients with pain were asked which treatment they received for their pain. In 14 patients this item was blank, 3 patients indicated they did not know the name of the treatment and 8 patients wrote ‘no treatment’. In total, 27 patients (45.7%) reported use of analgesic medication and 43 treatment items were scored: 23 non-opioid, 4 weak opioid, 8 strong and 8 other (antibiotics (n = 2), corticosteroids (n = 5) and physiotherapy (n = 1)). Patients were also asked to score the effect of treatment on pain relief on a scale ranging from 0% to 100%; the mean score was 43.5% (± 32.1), indicating a mean moderate relief of pain due to pain treatment.

Data on pain prescriptions were collected from the medical files of all patients. In the total group (patients with and without pain), 67 patients (45.0%) had one or more analgesic prescription (daily use); most frequently prescribed were non-opioid analgesics: paracetamol (25.4%) and non-steroidal anti-inflammatory drugs (15.9%). Analgesic prescription (daily use) was more frequent in patients with pain compared with those without pain (64% vs. 38%; p = 0.01). Analgesics ‘as needed’ were prescribed in 25.6% of the patients, with no differences between the two groups.

**Differences in symptom burden (prevalence and intensity) in patients with and without pain**

Almost all patients (91.3%) experienced moderate to severe dyspnoea with no differences between patients with and without pain (p = 0.37). After dyspnoea, fatigue, muscle weakness and symptoms of anxiety and/or depression were most prevalent. Patients with pain suffered more often from fatigue (p = 0.004), muscle weakness (p = 0.01), anorexia (p = 0.02) and symptoms of anxiety and/or depression (p = 0.04) (Table 2). Considering symptom intensity, patients with pain had significantly higher scores for all symptoms except for dyspnoea (Table 3).
Differences in health status in patients with and without pain

Patients with pain had significantly and clinically relevant worse disease-specific health status compared to patients without pain (Table 4). When analysing the differences in the scores on the three subdomains of the CCQ, only the CCQ_function subdomain showed significant and clinically relevant higher scores in patients with pain, compared to patients without pain.

Discussion

Main findings

The present study is the first to measure pain in patients hospitalized for AECOPD and indicated for post-acute PR and shows that 39.6% of these patients report pain with moderate to severe intensity and interference scores. These findings indicate that pain is also a relevant problem in this specific group of patients. Patients with pain also experienced a worse
disease-specific health status, compared to patients without pain, which was predominantly caused by more experienced limitations in functional status.

**Interpretation of findings and relation to literature**

In recent literature, two systematic reviews investigated pain prevalence in patients with stable COPD. Prevalences varied widely, from 32% to 88%, with a pooled prevalence of 66%. Compared to these results, we found a relatively low prevalence of pain. When comparing our results to individual studies that investigated pain in patients with similar characteristics (age, sex and lung function) that also used the BPI, more similarity was found. Lee et al. conducted a cross-sectional study in 64 patients (mean age 71 (+10) years; mean FEV1% predicted 37.9 (+14.9)) with stable COPD (outpatient clinic) and reported a pain prevalence of 41%. In two other studies, pain prevalence was 50% and 45% in patients with similar mean age (70.0 (+6.7) and 65.0 (+9.2) years) but slightly better lung function (mean FEV1% predicted 44.7 (+19.2) and 48 (+16%) respectively. However, in the cross-sectional study of Christensen et al., 61% of 258 COPD patients (mean age 63.4 (+9.4) years, mean FEV1% predicted 40.9 (+19.2)) reported pain. Interestingly, the authors concluded that lower stages of COPD were associated with (more) pain and more interference. The apparent paradoxical relationship between pain and lung function was also reported in our earlier review. This inverse relationship, probably also caused by selection bias, could be explained by the hypothesis that, in more severe COPD, other symptoms like dyspnoea are more distressing than pain, leading to more focus on dyspnoea and less on pain, also causing patients to be reluctant to spontaneously report pain. Furthermore, patients with more severe disease and worse health status might experience a ‘response shift’ in their perception of pain, as they may have had pain for a longer period of time. Response shift refers to the phenomenon that patients suffering from chronic diseases change their internal standards as their disease progresses. In summary, evidence from recent research together with the above outlined hypotheses indicates that our prevalence could be an underestimation.

Our data showed no difference in co-morbidity between patients with and without pain. Other studies reported co-morbidity as a risk factor for pain and correlations were shown between pain and the number of co-morbidities, but data are conflicting. Janssen et al. reported a high prevalence of thoracic pain (53.7%), but no correlation between the CCI and thoracic pain was found. A reason for this could be that the CCI measures co-morbidities in relation to mortality.

Regarding nutritional and functional status, several studies concluded that pain in COPD is associated with lower functional exercise capacity and higher BMI. Our results show no differences in functional and nutritional status between patients with and without pain. Furthermore, in the present study, decline of functional and nutritional status was probably dominant in comparison with the effect of pain.

In the present study, mean pain intensity and interference scores were relatively high compared to other reports in similar patients, but within the range of the mean scores reported in our review. Pain treatment was assessed by the self-reported BPI and by collecting prescription data from the medical files of all patients. Relief from pain treatment or medication provided was 43.5% (+32.1), which is comparable to the result of Christensen et al. (41.6% (+33.0)). Not many other studies on pain in COPD elaborated on pain treatment. In the study of Bentsen et al., 48.9% of the patients with pain received analgesics (patient reported), also similar to our results. When comparing this percentage with prescription data derived from the patient’s file, patient reported analgesic use seems to cause a considerable underestimation. However, still 36% of the patients with pain did not have any analgesic prescription. Results from recent literature on this topic, together with our data, indicate that pain treatment is probably suboptimal in terms of pain relief and prescription of analgetics in patients with COPD.

In patients with pain, total symptom burden was higher compared to patients without pain; they experienced more symptoms with worse intensity of which fatigue, muscle weakness and symptoms of anxiety and depression were most frequent and most severe. This is in line with earlier studies showing correlations between different symptoms and pain prevalence.
We found no difference in prevalence or severity of dyspnoea between patients with and without pain. This is an interesting result, as many studies in stable COPD found a relation between pain and dyspnoea. However, this finding can probably be explained by the overall high prevalence of dyspnoea in our study population, due to the acute state our patients were in.

The present study is in line with earlier studies reporting that pain is negatively associated with HRQoL and health status in stable COPD, as patients with pain in our study had a significantly and clinically relevant higher score on the CCQ. Interestingly, when looking at the mean scores on the subdomains of the CCQ, only the CCQ_function domain showed higher mean scores. However, no differences in more objective measurements of functional status (6MWT, BI) were found. Literature on the relation between pain and disease-specific health status measured with the CCQ is scarce. Two studies did not find an association between pain and outcomes of (subdomains of) the CCQ. The CCQ_function domain is known to correlate well with objective measurements of functional status in patients with COPD with similar age, lung function and functional status, but literature on this relationship in COPD patients with pain is completely lacking. Therefore, interpretation of this particular finding is difficult but could generate new hypotheses on this subject. First, when patients with pain experience more limitations than they objectively have, this might negatively influence their motivation for rehabilitation. Furthermore, rehabilitation might be more effective in these patients when specifically addressing pain experience, management and implications, also in relation to individual coping style. The study of Harrison et al. on the role of pain in PR from a qualitative perspective provides evidence that is in line with these hypotheses.

Conclusions and implications

Pain in patients hospitalized for AECOPD and indicated for post-acute PR is a relevant problem. Patients with pain experience more severe limitation in the function domain of their health status (CCQ) but no differences in objective measurements of functional status (6MWT, BI) were found. Pain in this specific group of patients needs more attention, as our study suggests that pain treatment is suboptimal. The reported prevalence of pain in patients hospitalized for AECOPD and indicated for post-acute PR is comparable to the prevalence of pain in the stable state. Therefore, incorporation of standard pain assessment in stable COPD and during exacerbations and post-acute PR is recommended, and patient education on pain in COPD and its possible implications is important. Further research should focus on assessing longitudinal data on pain in relation to exacerbations and post-acute PR as well as developing multi-domain pain treatment interventions that can be tested in (post-acute) PR programmes.

Acknowledgements

The authors would like to thank all participants and the staff and nurses of the Pulmonary Department of the Deventer Ziekenhuis and Isala Klinieken Zwolle, for their valuable contributions to this study. Special thanks go to the research assistants who selected the patients and collected the data.

Author contributions

The study was designed by Eléonore F van Dam van Isselt with participation of Karin H Groenewegen-Sipkema, Monica van Eijk, Niels H Chavannes and Wilco P Achterberg. Eléonore F van Dam van Isselt and Karin H Groenewegen-Sipkema wrote the manuscript, Monica van Eijk, Niels H Chavannes and Wilco P Achterberg reviewed the manuscript. All authors have given final approval of the version published.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was financially supported by Zorggroep Solis, Deventer and Stichting Achmea Gezondheidszorg (SAG), Apeldoorn (project code Z614).

**ORCID iD**

Eléonore F van Dam van Isselt  
https://orcid.org/0000-0002-5584-6295

**References**

1. van Dam van Isselt EF, Groenewegen-Sipkema KH and Spruit-van Eijk M, et al. Pain in patients with COPD: a systematic review and meta-analysis. *BMJ Open* 2014; 4: e005898. DOI: 10.1136/bmjopen-2014-005898.

2. Lee AL, Harrison SL, Goldstein RS, et al. Pain and its clinical associations in individuals with COPD: a systematic review. *Chest* 2015; 147: 1246–1258. DOI: 10.1378/chest.14-2690.

3. Borge CR, Wahl AK and Moum T. Association of breathlessness with multiple symptoms in chronic obstructive pulmonary disease. *J Adv Nurs* 2010; 66: 2688–2700. DOI: 10.1111/j.1365-2648.2010.05447.x.

4. HajGhanbari B, Holsti L, Road JD, et al. Pain in people with chronic obstructive pulmonary disease (COPD). *Respir Med* 2012; 106: 998–1005. DOI: 10.1016/j.rmed.2012.03.004.

5. Janssen DJ, Wouters EF, Parra YL, et al. Prevalence of thoracic pain in patients with chronic obstructive pulmonary disease and relationship with patient characteristics: a cross-sectional observational study. *BMC Pulm Med* 2016; 16: 47. DOI: 10.1186/s12890-016-0210-8.

6. Lohne V, Heer HC, Andersen M, et al. Qualitative study of pain of patients with chronic obstructive pulmonary disease. *Heart & Lung: J Crit Care* 2010; 39: 226–234. DOI: 10.1016/j.hrtlng.2009.08.002.

7. Lee AL, Harrison SL, Goldstein RS, et al. An exploration of pain experiences and their meaning in people with chronic obstructive pulmonary disease. *Physiother Theory Pract* 2018; 34(10): 765–772. DOI: 10.1080/09593985.2018.1425512.

8. HajGhanbari B, Garland SJ, Road JD, et al. Pain and physical performance in people with COPD. *Respir Med* 2013; 107: 1692–1699. DOI: 10.1016/j.rmed.2013.06.010.

9. Lee AL, Goldstein RS and Brooks D. Chronic pain in people with chronic obstructive pulmonary disease: prevalence, clinical and psychological implications. *Chronic Obstr Pulm Dis (Miami, Fla)* 2017; 4: 194–203. DOI: 10.15326/jcopdf.4.3.2016.0172.

10. Puhan MA, Gimeno-Santos E, Cates CJ, et al. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2016; 12: Cd005305. DOI: 10.1002/14651858.CD005305.pub4.

11. Aaron SD. Management and prevention of exacerbations of COPD. *BMJ (Clin Res Ed)* 2014; 349: g5237. DOI: 10.1136/bmj.g5237.

12. Groenewegen KH, Schols AM and Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest* 2003; 124: 459–467.

13. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, et al. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; 60: 925–931. DOI: 10.1136/thx.2005.040527.

14. Harrison SL, Lee AL, Elliott-Button HL, et al. The role of pain in pulmonary rehabilitation: a qualitative study. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 3289–3299. DOI: 10.2147/copd.s145442.

15. Global Initiative for Chronic Obstructive Lung Disease (GOLD). From the global strategy for the diagnosis, management and prevention of COPD, http://goldcopd.org (2017, accessed 1 February 2014).

16. Charlson ME, Charlson RE, Peterson JC, et al. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol* 2008; 61: 1234–1240. DOI: 10.1016/j.jclinepi.2008.01.006.

17. Schols AM, Broekhuizen R, Weling-Scheepers CA, et al. Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2005; 82: 53–59.

18. Cleeland CS and Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singapore* 1994; 23: 129–138.

19. Reid WD, Chen YW, HajGhanbari B, et al. Validation of the brief pain inventory in people with chronic obstructive pulmonary disease. *Eur Respir J* 2016; 48: PA3735. DOI: 10.1183/13993003.congress-2016.

20. Leung L. From ladder to platform: a new concept for pain management. *J Prim Health Care* 2012; 4: 254–258.

21. Clark N, Fan VS, Slatore CG, et al. Dyspnea and pain frequently co-occur among Medicare managed care recipients. *Ann Am Thorac Soc* 2014; 11: 890–897. DOI: 10.1513/AnnalsATS.201310-369OC.
22. Chen YW, Camp PG, Coxson HO, et al. A comparison of pain, fatigue, dyspnea and their impact on quality of life in pulmonary rehabilitation participants with chronic obstructive pulmonary disease. *COPD* 2018; 15: 65–72. DOI: 10.1080/15412555.2017.1401990.

23. Cheung G, Patrick C, Sullivan G, et al. Sensitivity and specificity of the geriatric anxiety inventory and the hospital anxiety and depression scale in the detection of anxiety disorders in older people with chronic obstructive pulmonary disease. *Int Psychogeriatr* 2012; 24: 128–136. DOI: 10.1017/s1041610211001426.

24. Collin C, Wade DT, Davies S, et al. The Barthel ADL index: a reliability study. *Int Disabil Stud* 1988; 10: 61–63.

25. Sainsbury A, Seebass G, Bansal A, et al. Reliability of the Barthel index when used with older people. *Age Ageing* 2005; 34: 228–232. DOI: 10.1093/ageing/afi063.

26. Puente-Maestu L, Palange P, Casaburi R, et al. Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. *Eur Respir J* 2016; 47: 429–460. DOI: 10.1183/13993003.00745-2015.

27. van der Molen T, Willemse BW, Schokker S, et al. Development, validity and responsiveness of the clinical COPD questionnaire. *Health Qual Life Outcomes* 2003; 1: 13.

28. Kocks JW, Tuinenga MG, Uil SM, et al. Health status measurement in COPD: the minimal clinically important difference of the clinical COPD questionnaire. *Respir Res* 2006; 7: 62. DOI: 10.1186/1465-9921-7-62.

29. Bentsen SB, Rustoen T and Miaskowski C. Prevalence and characteristics of pain in patients with chronic obstructive pulmonary disease compared to the Norwegian general population. *J Pain: Off J Am Soc Pain Manag Nurs* 2011; 12: 539–545. DOI: 10.1016/j.jpain.2010.10.014.

30. Christensen VL, Holm AM, Kongerud J, et al. Occurrence, characteristics, and predictors of pain in patients with chronic obstructive pulmonary disease. *Pain Manag Nurs: Off J Am Soc Pain Manag Nurs* 2016; 17: 107–118. DOI: 10.1016/j.pmn.2016.01.002.

31. Schwartz CE and Sprangers MA. Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. *Soc Sci Med* (1982) 1999; 48: 1531–1548.

32. Bentsen SB, Rustoen T and Miaskowski C. Differences in subjective and objective respiratory parameters in patients with chronic obstructive pulmonary disease with and without pain. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 137–143. DOI: 10.2147/copd.s28994.

33. Borge CR, Wahl AK and Moum T. Pain and quality of life with chronic obstructive pulmonary disease. *Heart & Lung: J Crit Care* 2011; 40: e90–e101. DOI: 10.1016/j.hrtlng.2010.10.009.

34. Bentsen SB, Gundersen D, Assmus J, et al. Multiple symptoms in patients with chronic obstructive pulmonary disease in Norway. *Nurs Health Sci* 2013; 15: 292–299. DOI: 10.1111/nhs.12031.

35. Bentsen SB, Miaskowski C, Cooper BA, et al. Distinct pain profiles in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2018; 13: 801–811. DOI: 10.2147/copd.S150114.

36. Chen YW, Camp PG, Coxson HO, et al. Comorbidities that cause pain and the contributors to pain in individuals with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* 2017; 98: 1535–1543. DOI: 10.1016/j.apmr.2016.10.016.

37. van Dam van Isselt EF, Spruit M, Groenewegen-Sipkema KH, et al. Health status measured by the clinical COPD questionnaire (CCQ) improves following post-acute pulmonary rehabilitation in patients with advanced COPD: a prospective observational study. *NPJ Prim Care Respir Med* 2014; 24: 14007. DOI: 10.1038/njppcm.2014.7.