Review Article

Chronic Respiratory Disease

Chronic Respiratory Disease
Volume 19: 1–14

DOI: 10.1177/14799731221105518
journals.sagepub.com/home/crd
SAGE

The prevalence and assessment of pain and dyspnoea in acute exacerbations of COPD: A systematic review

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Abstract

Background: Dyspnoea and pain are symptoms of chronic obstructive pulmonary disease (COPD). This review focused upon pain and dyspnoea during hospital admissions for acute exacerbations of COPD (AECOPD), with the aim of examining prevalence, assessment, clinical associations, and researcher-reported implications of these symptoms.

Methods: Four electronic databases were searched from inception to 31 May 2021. Full text versions of studies were assessed for methodological quality and data were extracted independently by two reviewers. Where data permitted, pooled prevalence of pain and dyspnoea were calculated by meta-analysis.

Results: Four studies were included. The pooled prevalence of pain and dyspnoea was 44% (95% confidence interval (CI) 35%–52%) and 91% (95% CI 87%–94%) respectively. An array of instruments with varying focal periods were reported (pain: six tools, dyspnoea: four tools). Associations and clinical implications between the two symptoms at the time of hospital admission were rarely reported.

Conclusions: Few studies reported prevalence of pain and dyspnoea during an AECOPD. A greater understanding into the prevalence, intensity and associations of these symptoms during AECOPD could be furthered by use of standardised assessment tools with clearly defined focal periods.

Keywords

Chronic obstructive pulmonary disease, exacerbation, pain, dyspnoea, scale

Date received: 26 November 2021; accepted: 12 April 2022

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterised by acute exacerbations. An exacerbation of COPD is an acute worsening of respiratory symptoms[1] and is characterised by changes in an individual's baseline dyspnoea, cough and/or sputum beyond day-to-day variations, which may require a change in medication and/or admission to hospital.[2]

While dyspnoea is recognised as the most characteristic feature of COPD with a reported prevalence of up to 93%,[3] pain has also been identified as a symptom affecting between 21% and 85% of people in a stable state.[4–6] In people

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with stable COPD, pain exhibits a negative impact on mood and contributes to increased fatigue, heightened anxiety and depression, difficulty clearing secretions, fear-avoidance behaviour and poorer quality of life.[7–10] Sensations of pain and dyspnoea are known to originate in afferent nervous systems, through which threat to the body is detected.[11] The sensory input generated by dyspnoea and pain have been found to be processed in similar regions of the brain, specifically the insula, dorsal anterior cingulate cortex, amygdala and medial thalamus. These regions are known to be involved in the processing of fear and anxiety, amongst other emotions.[12] These similarities in neural pathways and central structures explain why pain and dyspnoea are both described as unpleasant sensory and emotional experiences which are associated with sensory and affective dimensions.[12–15]

In stable COPD, a positive correlation between the presence of pain and dyspnoea has been demonstrated, both of which were found to negatively impact quality of life,[16] with individuals experiencing pain reporting higher dyspnoea scores compared to those without pain.[10] Current knowledge concerning the interaction between pain and dyspnoea has focused on people in the stable state of COPD. However, the clinical management of COPD varies between stable state and acute exacerbations, in response to changes in presenting symptoms.[2] These presenting symptoms commonly include an increase in dyspnoea, a known characteristic feature of acute exacerbations and a higher pain intensity and differing pain locations, compared to a stable condition.[17] These features have the potential to inform treatment decisions and subsequently influence recovery. However, the prevalence of both dyspnoea and pain in the same individual in this clinical state is comparatively underexplored. In light of the symmetry in neurophysiology and sensory and affective dimensions of each symptom, further understanding of the interactions between pain and dyspnoea and their clinical implications in those with an acute exacerbation of COPD is required. This review is the first step towards understanding the relationship between both symptoms in this population, with the potential to inform their co-influence on treatment efficacy and on other clinical outcomes, including duration of recovery.

Pain and dyspnoea in COPD are recognised as complex and aversive symptoms. To capture the complexity of each symptom, a number of tools have been developed to assess severity, impact and behaviour of these symptoms. However, it is not clear which instruments have been used to assess pain and dyspnoea in those with an acute exacerbation.

The primary aim of this review was to investigate the prevalence of pain and dyspnoea in people admitted to hospital with an acute exacerbation of COPD. The secondary aims were to (1) identify the tools and corresponding focal periods applied to assess pain and dyspnoea in acute exacerbations of COPD, and (2) to identify the clinical associations and researcher-reported implications of pain and dyspnoea, including the interaction between both symptoms in this clinical state.

Method

The protocol for this systematic review was registered with Prospero (CRD42020182386). The process for this systematic review was undertaken in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]

A systematic search of four databases (EMBASE, MEDLINE, Cochrane Library, CINAHL) was undertaken by one reviewer (S.Y.C). The search strategy for MEDLINE is referenced in Appendix 1 and was adapted for other databases. Searches were conducted from database inception to 31 May 2021. The years of inception for EMBASE, MEDLINE, Cochrane Library and CINAHL were 1974, 1966, 1993 and 1961 respectively.

After duplicates were removed, titles and abstracts of identified records were independently screened by two reviewers (S.Y.C. and A.L.L.) using Covidence.[19] Studies in English were considered for inclusion, as there was no scope for translation of other languages. Full-text versions of potentially eligible studies were retrieved and independently assessed for inclusion by the two reviewers, according to the inclusion criteria in Table 1. Studies were eligible for inclusion if prevalence of pain and dyspnoea were both reported. Included studies were peer reviewed. Abstracts, and conference abstracts were included as long as they provided sufficient relevant information regarding the prevalence of pain and dyspnoea. Any disparity regarding eligibility at either the screening or full-text review stage was resolved by a consensus meeting between the two reviewers.

Data extraction was completed by reviewer S.Y.C., collated in Microsoft Excel and independently checked by reviewer A.L.L. Extracted data included study and patient demographics, prevalence of pain and dyspnoea, as well as instruments used, focal periods for symptom presence and clinical associations and implications reported for both pain and dyspnoea. The definition or nature of pain was not restricted, as it is recognised that pain may arise from different sources.[6] For this reason, pain may have been acute or chronic in nature, with a mix of possible aetiologies. This approach was adopted based on current knowledge of types and possible causes of pain in those in a stable clinical state, with a mix of pain experienced.[20] The focal period was identified as the period of time over which the assessment of each symptom was measured. For example, the Brief Pain Inventory (BPI) asks participants to rate their pain intensity as recalled over the past week.[21] Therefore, the focal period for the BPI is one week. Researcher-reported implications were defined as the clinical implications stated by authors within the publication.

Table 1. Study inclusion criteria.

Criterion	Inclusion criteria
Participants	People diagnosed with chronic obstructive pulmonary disease, admitted to hospital with an acute exacerbation of their respiratory condition
Types of studies	Observational cohort studies Prospective or retrospective studies Randomised controlled trials Crossover studies
Primary outcomes	Prevalence of pain AND prevalence of dyspnoea as measured by questionnaire items, self-report scales, such as a numerical rating scale or visual analogue scale or validated instruments which provide a separate measure for the presence of pain and/or dyspnoea
Secondary outcomes	Instruments and focal periods for symptom presence reported to assess pain and/or dyspnoea Clinical associations and researcher reported implications of pain and/or dyspnoea including intensity, location, cause, relationship with other symptoms, relationship to quality of life or health status and use of analgesia

All included studies were appraised using the risk of bias assessment tool described by Hoy et al.,[22] which is specific to the assessment of prevalence studies. The tool assesses the risk of bias across four areas; selection bias, non-response bias, measurement bias and bias related to analysis. This was completed independently by two reviewers (S.Y.C and A.L.L), with any disagreements resolved during a consensus meeting.

Where data permitted, pooled prevalence of pain and dyspnoea were calculated using MetaXL 1.3 in Microsoft Excel (EpiGear International Pty LTD). The data were first transformed using the variance stabilising double arcsine transformation.[23] Using a quality effects model, the prevalence and 95% confidence interval for both pain and dyspnoea were calculated. This model was selected over the fixed or random effects model to explicitly address heterogeneity in pooled proportions caused by differences in study quality and distribution, with greater weighting given to studies of higher methodological quality.[24] Heterogeneity was assessed using the Q and I^2 measures calculated by MetaXL 1.3. Study findings that were not able to be pooled were reported narratively.

Deviations to published protocol

The Downs and Black tool was originally selected to assess the risk of bias of included studies, prior to the identification of studies meeting the inclusion criteria. Based on the types of included studies, the tool by Hoy et al. was utilised as it is specific to the assessment of risk of bias in prevalence studies.

Results

Study selection

A total of 1300 potentially eligible articles published before 31 May 2021 were identified. Following removal of 144 duplicates, 1156 titles and abstracts were screened, from which 34 full-text articles were further evaluated against the inclusion criteria (Table 1). Four studies published between 2000 and 2019 were eligible for inclusion within this review (Figure 1). These included two prospective studies, one case-control study and one cross-sectional observational study. The number of participants in the included studies ranged from 32 to 1008. Disease severity of participants was reported in three studies[25-27] with measures of forced expiratory volume in one second indicating participants had severe airflow limitation (Forced expiratory volume in one second (FEV_1) mean ranging from 35 to 40% of predicted value).[1] Study characteristics and demographic data are presented in Table 2.

Risk of methodological bias assessment

Results from the risk of bias assessment are outlined in Table 3. All studies were assessed as having a sampling frame that was a true or close representation of the target population. As all studies recruited from a small number of sites or a single hospital, it was unclear whether the sample was closely representative of the national population of the study's country of origin with regard to demographic data relevant to people with COPD, including age and co-morbidity. Random sampling did not occur in any studies and all studies were identified as being at high risk of non-response bias, as no information was provided about potential participants who were approached for inclusion but did not participate. One study[27] was classed as low risk of bias with regard to the instruments used, as it applied valid and reliable instruments.

Measurement tools and focal periods of assessment for pain

The scales and tools used by each study to measure pain, dyspnoea, function, other symptoms, quality of life and

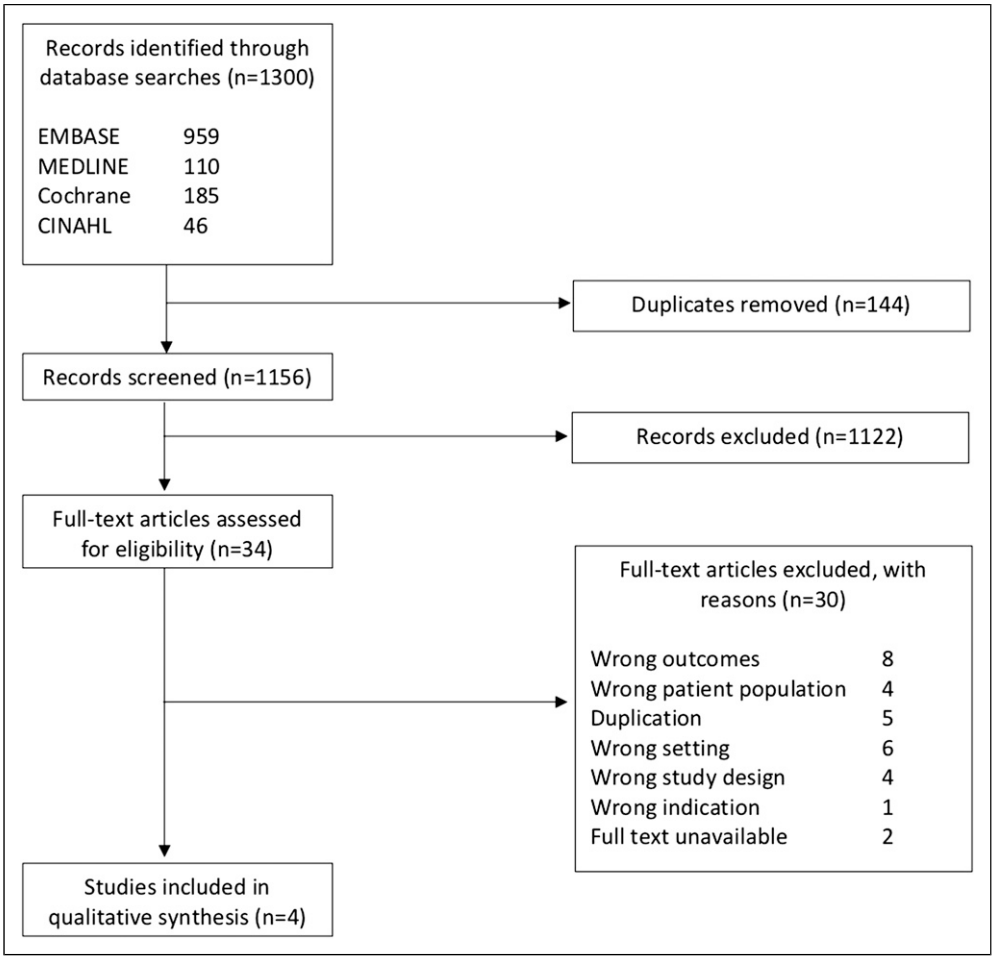

Figure 1. Study flow diagram from identification of records to inclusion of studies. CINAHL: Cumulative Index to Nursing and Allied Health Literature; EMBASE: Excerpta Medica Database.

Table 2. Study characteristics and demographic data.

Study	Country	Study type	Hospital admission for AECOPD	No. of participants	Age, years	Sex, male/female	FEV_1 % pred
Claessens et al. 2000	United States of America	Prospective	Yes	1008	70[a]	517/491	NR
Hosseini et al. 2015	Iran	Case control	Yes	170	66 (9)	93/77	40 (23)
Srinivasan et al. 2019	Australia	Prospective	Yes	32	70 (9)	18/14	37 (13)
van Dam van Isselt et al. 2019	Netherlands	Cross- sectional observational	Yes	149	71 (8)	73/76	35 (13)

Data are mean (SD), unless indicated.
AECOPD = acute exacerbation of COPD; FEV_1 = forced expiratory volume in one second; NR = not reported; % pred = percentage of predicted.
[a]reported as median.

demographic data are outlined in Table 4. Each of the studies used a different method to establish the prevalence of pain. Van Dam van Isselt et al.[27] defined the presence of pain according to the BPI. Srinivasan et al.[26] applied the Condensed Memorial Symptom Assessment Scale (CMSAS), in addition to a more detailed pain assessment to identify the site, intensity and cause of pain.[26] Both the BPI and CMSAS have focal periods of the past 7 days. Hosseini

Table 3. Assessment of risk of bias of included studies.

	Study			
	Claessens et al. 2010	Hosseini et al. 2015	Srinivasan et al. 2019	van Dam van Isselt et al. 2019
Was the study's target population a close representation of the national population in relation to relevant variables?	No	No	No	No
Was the sampling frame a true or close representation of the target population?	Yes	Yes	Yes	Yes
Was some form of random selection used to select the sample, or was a census undertaken?	No	No	No	No
Was the likelihood of nonresponse bias minimal?	No	No	No	No
Were data collected directly from the subjects (as opposed to a proxy)?	No	Yes	Yes	Yes
Was an acceptable case definition used in the study?	No	No	No	Yes
Was the study instrument that measured the parameter of interest shown to have validity and reliability?	No	No	No	Yes
Was the same mode of data collection used for all subjects?	No	Yes	Yes	Yes
Was the length of the shortest prevalence period for the parameter of interest appropriate?	No	Yes	Yes	Yes
Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	No	Yes	Yes	Yes

Key to scoring (14): Yes = yes (low risk), No = no or insufficient information to permit a judgment (high risk).

et al.[23] used diary cards to record changes in symptoms, including pain, over the past 48 h. Claessens et al.[28] included two questions about pain but did not specify the corresponding focal period. None of the included studies utilised a subdomain of a quality of life scale in their assessment of pain.

Prevalence of pain

Reported prevalence of pain ranged from 21% to 56% (Table 5). Of the four included studies, one study [28] reported the prevalence of pain, however upon analysis of the included data, the number of participants to whom the prevalence was relevant could not be established. For this reason, this study was excluded from the meta-analysis. The pooled prevalence from three studies was 44% (95% confidence intervals (CI) 36%–52%) (Figure 2(a)). Heterogeneity measures of Q = 2.99 and I^2 = 33% suggests a low to moderate degree of variability between studies.

Characteristics and associations of pain

The nature of the pain experienced was not identified in any of the included studies. The characteristics of pain (intensity and/or location) during an acute exacerbation were reported in two studies.[26,27] Average pain of 4.8 on an intensity scale from zero to 10 was reported in one study.[26] Similarly, Van Dam van Isselt et al.[27] reported a mean score of pain "right now" at 4.1 points as measured by the BPI pain intensity scale. Two studies reported on the location of pain,[26,27] with commonly reported locations being chest, back and shoulders/arms (Table 5). According to van Dam van Isselt et al.,[27] BPI derived pain interference scores were highest for interference with normal work, walking ability and general ability (Table 5).

One study comparing demographic data between those with and those without pain reported no difference in age, sex or disease characteristics (FEV_1, comorbidity score, nutritional status and smoking status) between the two groups.[27] The percentage of participants with muscle pain was higher in those infected with a respiratory virus compared to uninfected participants.[25] Use of analgesia was reported in one study,[27] with paracetamol being the most commonly used analgesic.

Van Dam van Isselt et al.[27] examined the effect of pain on disease-specific quality of life; those with pain had significantly poorer disease-specific health status as measured by the Clinical COPD Questionnaire. In an analysis of subdomains, only the function subdomain was worse in patients with pain, compared to those without pain.[27] The prevalence and intensity of both anxiety and depression as well as fatigue, muscle weakness and anorexia were higher in those with pain compared to those without pain.[27] While there was no difference in the prevalence of insomnia between those with and those without pain, the intensity of insomnia was higher in those with pain.[27]

Table 4. Measures and scales used in included studies.

		Claessens et al. 2000	Hosseini et al. 2015	Srivinasan et al. 2019	van Dam van Isselt et al. 2019
Demographic	Respiratory Function Test		x	x	x
	Global Obstructive Lung Disease Stage		x		
	Body Mass Index		x		x
	Fat-Free Mass Index				x
	Acute Physiology Score	x			
	Tobacco use (pack years)		x		
	Smoking status: Yes/no				x
	Charlson Co-morbidity Index				x
Function	Katz Activities of Daily Living Scale	x			
	Six Minute Walk Test				x
	Barthel Index				x
Pain	Interview questions: How severe is the pain? How much of the time do you experience pain?	x			
	Diary cards[a]		x		
	Brief Pain Inventory				x
	Condensed Memorial Symptom Assessment scale			x	
	Detailed pain assessment: site, pain [0–10], cause			x	
Dyspnoea	Interview question: How severe is the dyspnoea? How much of the time do you experience dyspnoea?	x			
	Diary cards[a]		x		
	Condensed Memorial Symptom Assessment Scale			x	
	Modified Medical Research Council Dyspnoea Scale				x
Other symptoms	Profile of Mood States	x			
	Hospital Anxiety and Depression Scale				x
	Condensed Memorial Symptom Assessment Scale			x	
	Presence of, and degree of bother[b]: Cough			x	
	Presence of, and degree of bother[b]: Sputum			x	
	Presence of, and degree of bother[b]: Anxiety			x	
	Numerical Rating Scale: Fatigue				x
	Numerical Rating Scale: Muscle weakness				x
	Numerical Rating Scale: Insomnia				x
	Numerical Rating Scale: Anorexia				x
QOL	Question: Rate the overall quality of life[#]	x			
	Clinical COPD Questionnaire				x

COPD = chronic obstructive pulmonary disease; QOL = quality of life.
[a]recording change in symptoms over last 48 h.
[b]5-point Likert scale.

Measurement tools and focal periods for assessment of dyspnoea

Each of the studies used a different method to establish the prevalence of dyspnoea (Tables 4 and 6).

Only one study used a validated tool for people with COPD: the modified Medical Research Council (mMRC) Dyspnoea Scale.[27] The specific focal period for the mMRC was not specified, only that it was completed by participants during their admission with exacerbation.[27] Srinivasan et al.[26] assessed the presence of dyspnoea within 72 hours of admission using the CMSAS, which has a focal period of the past 7 days. Claessens et al.[28] included two questions about dyspnoea, but the precise focal period assessed was unclear. Hosseini et al.[25] used a diary card for monitoring of changes in symptoms, including dyspnoea, over the preceding 48 hours.

Prevalence of dyspnoea

Reported prevalence of dyspnoea ranged from 56% to 91% (Table 6). Of the four included studies, while one[28] reported on the prevalence of dyspnoea, the means by which the prevalence was calculated and the number of participants to whom this prevalence applied was not clear. Therefore, this study was excluded from the meta-analysis. The overall pooled prevalence was 91% (95% CI 87%–94%) (Figure 2(b)). Heterogeneity measures of

Table 5. Prevalence, scales, focal periods, characteristics and associations of pain.

			Claessens et al. 2000	Hosseini et al. 2015	Srinivasan et al. 2019	van dam van isselt et al. 2019
Scales			Interview questions	Diary cards	Condensed Memorial Symptom Assessment Scale Detailed pain assessment	Brief Pain Inventory
Focal period			NR	Past 48 hours	Past 7 days	Past 7 days
Prevalence of pain [*n*=]			21% #	44% (*n* = 75)	56% (*n* = 18)	39.6% (*n* = 59)
Pain characteristics	**Intensity** [Mean±SD unless otherwise reported]		Moderate/extremely severe at least half of the time	NR	4.8 ± 2.7	Right now = 4.1 ± 3.1 Worst =6.4 ± 2.5 Least =2.7 ± 2.3 Average = 4.3 ±2.3
	Location [total number *n*=]		NR	NR	31	94
	Common location (%)	Chest			23%	22.3%
		Upper back				35.1%
		Lower back				17%
		Back			23%	
		Shoulders			13%	
		Upper leg				8.6%
		Lower leg				5.3%
		Head				5.3%
		Upper limbs				3.2%
		Abdomen				3.2%
Associations			NR		Patient reported causes of pain: cough, arthritis	

(continued)

Table 5. (continued)

			Claessens et al. 2000	Hosseini et al. 2015	Srinivasan et al. 2019	van dam van isselt et al. 2019
Differences between participants	**Muscle pain prevalence**	Respiratory virus positive versus respiratory virus negative		77% vs 14% ($p < 0.05$*)		
	Symptom prevalence [with pain versus without pain]	Dyspnoea				88.1% vs 93.3% ($p = 0.37$)
		Fatigue				94.5% vs 75.6% ($p = 0.004$*)
		Muscle weakness				80.0% vs 58.0% ($p = 0.01$*)
		Insomnia				67.3% vs 53.1% ($p = 0.11$)
		Anorexia				56.4% vs 35.8% ($p = 0.02$*)
		Anxiety & depression				70.7% vs 52.8% ($p = 0.04$*)
	Symptom intensity [mean±SD] [with pain versus without pain]	Fatigue				72.6 ± 20.4 vs 56.8 ± 25.7 ($p < 0.001$*)
		Muscle weakness				56.7 ± 25.9 vs 45.4 ± 28.1 ($p = 0.02$*)
		Insomnia				49.9 ± 33.5 vs 36.3 ± 28.0 ($p = 0.01$*)
		Anorexia				46.1 ± 22.9 vs 27.8 ± 20.0 ($p = 0.001$*)
		Anxiety				8.9 ± 4.5 vs 7.2 ± 4.4 ($p = 0.03$*)
		Depression				8.3 ± 4.6 vs 6.9 ± 3.8 ($p = 0.07$)
	Disease-specific health status score [mean±SD] [with pain versus without pain]	Total score				3.9 ± 1.0 vs 3.4 ± 1.1 ($p = 0.04$*)
		Function subdomain				4.4 ± 1.1 vs 3.9 ± 1.3 ($p = 0.04$*)

= *n* unable to be established from available data; * = significant difference ($p \leq 0.05$); NR = Not reported; SD = standard deviation.

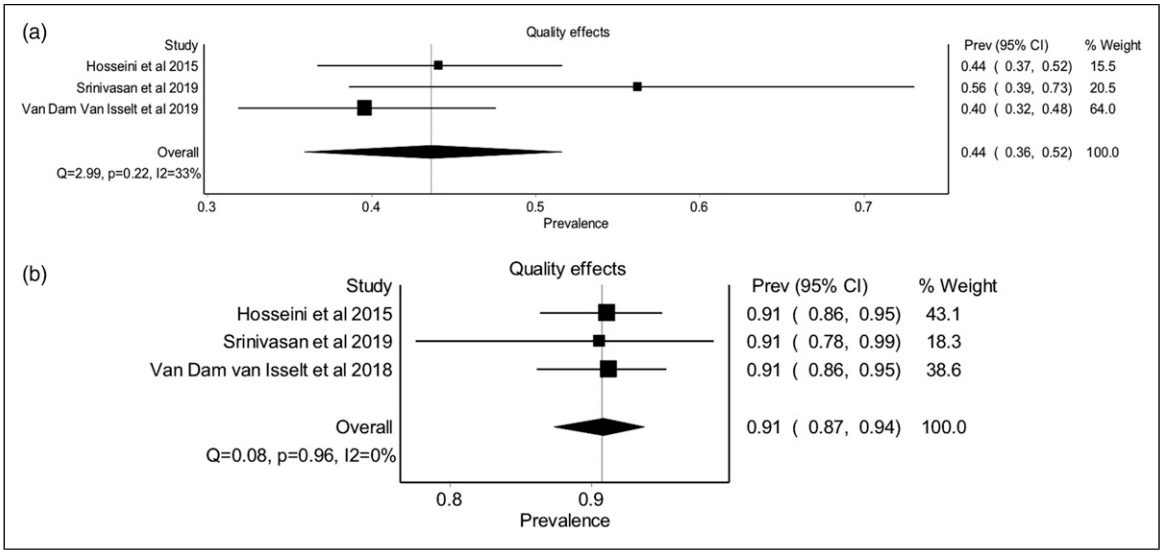

Figure 2. Pooled prevalence of (a) pain reported in included studies; and (b) dyspnoea reported in included studies.

$Q = 0.08$ and $I^2 = 0$ indicate a low level of heterogeneity across studies.

Characteristics and associations of dyspnoea

No significant difference in dyspnoea prevalence or intensity was reported between those with and those without pain (Table 6).[27] Breathlessness (sic) was both the most prevalent and bothersome symptom reported on the CMSAS in one study.[26] An increase in dyspnoea was present both in participants infected with respiratory virus and those who were respiratory virus negative, but no statistical comparison was reported[25] (Table 6).

Clinical implications and interactions of pain and dyspnoea reported within studies

A single study[27] reported the implications of pain in exacerbations of COPD, stating that "Pain in this specific group of patients needs more attention, as our study suggests that pain treatment is suboptimal" and that "incorporation of standard pain assessment in stable COPD and during exacerbations and post-acute pulmonary rehabilitation is recommended".

Discussion

This systematic review aimed to identify the prevalence of both pain and dyspnoea experienced concurrently in people admitted to hospital with an exacerbation of COPD. Using all available data, pooled prevalence of pain and dyspnoea was 44% and 91% respectively. An array of different outcomes measures with varying time frames were applied within the studies for pain (six tools) and dyspnoea (four tools) with limited synthesis of clinical characteristics at the time of a hospital admission. The reporting of clinical associations, implications of both symptoms and their interaction in acute exacerbations of COPD was rare.[27]

Less than 10% of clinical practice guidelines for management of COPD make reference to pain as a symptom affecting this population.[29] In a recent systematic review of outcome measures used in the management of exacerbations of COPD,[30] pain was not identified as a symptom that is evaluated in this disease state. Of two studies to date which examined pain during an acute exacerbation of COPD independent of the presence of dyspnoea, the prevalence ranged from 31.3% to 96%.[17, 31] The clinical priority in management of COPD exacerbations is aimed at resolving the underlying acute physiological problems including airflow limitation, mucus production, infection, hypoxia, hypercarbia and acidosis.[2] With the focus on addressing these potentially life-threatening problems, pain may be considered to be of comparatively lower clinical importance, resulting in it being less frequently considered as a feature of an exacerbation of COPD. The failure to recognise pain as a symptom of COPD and the limited investigation into the co-existence and interaction between pain and dyspnoea may account for the very small number of studies investigating the prevalence of both symptoms experienced concurrently in individuals with acute exacerbations of COPD.

In the small number of included studies, there was a wide range in the reported prevalence of pain. This variability may be attributable to variations in scales, different focal periods and diverse definitions to determine the presence of pain. Currently, there does not appear to be consensus for optimal tools to assess pain in people living with COPD (stable or exacerbated states). A systematic review investigating the tools used for assessment of pain in stable state COPD found the BPI (short

Table 6. Prevalence, scales, focal periods, characteristics and associations of dyspnoea.

Study	Prevalence of dyspnoea	Scales for measurement of dyspnoea	Focal period for measurement of dyspnoea	Dyspnoea characteristics	Dyspnoea associations
Claessens et al. 2000	56%[a]	Interview questions	NR	Dyspnoea was reported as moderate or extremely severe at least half of the time	NR
Hosseini et al. 2015	91% (*n* = 155)	Diary cards	Past 48 hours	NR	Dyspnoea prevalence in those who are respiratory virus positive (98.7%) Dyspnoea prevalence in those who are respiratory virus negative (84.2%)
Srinivasan et al. 2019	91% (*n* = 29)	Condensed Memorial Symptom Assessment Scale	Past 7 days	Breathlessness as physical symptom = most prevalent (91%) = most bothersome (median 3.2 (IQR 1.6–4.0) points)	NR
van Dam van Isselt et al. 2019	91% (*n* = 136)	Modified Medical Research Council Dyspnoea Scale	NR	Moderate to severe dyspnoea (≥2 on mMRC dyspnoea scale)	Dyspnoea prevalence in those with pain (93.3%) vs without pain (88.1%), NSD ($p = 0.37$) Dyspnoea intensity in those with pain (mean 3.1 [SD1.0]) vs without pain (mean 3.1 [SD1.0]), NSD ($p = 0.60$)

mMRC = modified medical research council; NR = not reported; NSD = no significant difference $p \geq 0.05$.
[a]*n* unable to be established from available data.

form) was most commonly used, with numerical rating scales, McGill Pain Questionnaire and BPI (long form) also used to quantify pain intensity.[6] The focal periods in the studies in our review were commonly defined by the tools used, and varied from 48 hours, seven days or no defined time frame. While the choice of focal period may be dictated by the tool selected, this symptom is likely to vary in severity over the course of an acute exacerbation, with the potential for greater prevalence and severity early in an admission. This is illustrated by Maignan et al.,[17] who reported a pain prevalence of 92%, with the measurement completed within six hours of admission for an acute exacerbation of COPD. The available information about the intensity and location of pain during exacerbations is drawn from two studies.[26,27] While using different tools, both studies included assessment of pain intensity on a numerical rating scale and reported pain to be between 4 and 5 (from 0–10) during exacerbation. Common locations of pain included the chest, back and shoulders.[26,27] This is consistent with the findings of Maignan et al.,[17] who reported the chest as the predominant location of pain during exacerbations of COPD, together with the upper back and trunk. Further investigation into the experience of pain at various time points during exacerbation, using validated tools such as the BPI (short form) or McGill Pain Questionnaire would allow assessment of the presence and prevalence of pain within tightly defined focal periods, and would provide valuable insight into the characteristics and nature of pain throughout an exacerbation. This will further the understanding of the prevalence of pain and symptom behaviour in this disease state.

Similarly, the tools and associated focal periods used to assess dyspnoea varied between studies, with only one study assessing intensity. As dyspnoea is a key characteristic of exacerbations of COPD,[2] it is unsurprising that the prevalence of dyspnoea was consistently high in all studies. A greater understanding of the fluctuation in prevalence, intensity and nature of dyspnoea could be gained from the use of multidimensional dyspnoea instruments such as the Multidimensional Dyspnoea Profile to quantify and characterise the experience of dyspnoea during an exacerbation of COPD. A recent study[32] of dyspnoea during an inpatient hospital admission reported that patients with mixed diagnoses including respiratory disease who reported any level of dyspnoea were at increased risk of death during that admission, with the severity of dyspnoea proportional to the risk of mortality. This further emphasises the importance of exploring this symptom in this clinical state.

Little is known about whether pain experienced by people during exacerbations represents a new symptom or whether it is of a differing nature and intensity to that experienced during stable state. Maignan et al.[17] reported the prevalence and intensity of pain as significantly higher during exacerbations compared to stable state, with differing pain locations between the two disease states. Further exploration of differences in pain prevalence and experience between disease states would broaden our understanding of this symptom during exacerbations of COPD.

There is very little evidence about the clinical associations of pain during an exacerbation of COPD. Only one study[27] indicated that the prevalence and intensity of other symptoms such as fatigue, anxiety and weakness was higher in those with pain. While these preliminary findings align with reports of the clinical association between pain and other symptoms (including dyspnoea) in those in a stable disease state,[5,6] the paucity of information about the clinical associations, impacts and benefits of treatment of pain during exacerbations, likely stems from the under-recognition of pain as a symptom in this disease state.

With such limited evidence about the prevalence and experience of co-occurring pain and dyspnoea during exacerbations of COPD, there have been limited clinical implications drawn from the available research. The recommendations by van Dam van Isselt et al.[27] highlight that for many people with COPD, pain is a relevant problem but is under-assessed, under-treated and not commonly factored into patient care during an acute exacerbation. For example, discharge care bundles are sets of evidence-based practices targeted at improving patient outcomes on discharge following exacerbations, and that have been shown to reduce readmission rates.[33] Discharge criteria from acute care following exacerbations are predominantly focused on resolution of dyspnoea, reduction in medication and oxygen requirements, return to baseline function and follow-up arrangements.[2] A systematic review of discharge care bundles explored the individual interventions included, but assessment and strategies for pain were not singled out, nor considered in conjunction with symptoms of dyspnoea and it is unclear if pain was considered within the education and care plans for self-management strategies.[33] While the current knowledge about the relationship between pain and quality of life, function and other symptoms[6] supports the recommendations for pain assessment to be included in clinical care of people with COPD,[5] a more robust understanding of these relationships specifically during exacerbations will give more strength to this recommendation.

Pain and dyspnoea have been identified as two of the most frequent and serious symptoms experienced by those requiring palliative care, with the need to control these symptoms recognised as an important part of reducing suffering.[34] In contrast, treatment of COPD exacerbations is directed at resolving the underlying physiological problems.[2] In those with severe COPD, a symptom-based management approach during exacerbation may increase the recognition of pain as a symptom affecting this patient cohort.

There are several limitations of this review. There were a very small number of studies eligible for inclusion that reported on the prevalence of both pain and dyspnoea. There was considerable variability in the sample size of the included studies, with only one study powered for the primary aim of investigating the prevalence of pain. There was little consistency between scales and focal periods used to assess pain and dyspnoea, making it challenging to synthesise information. Included studies were limited to those available in English, retrieved from four databases, but the impact of these limitations is unknown. Assessment of publication bias was not undertaken, as it is not recommended for a review of less than 10 studies.[35] Selection bias is unlikely to have impacted the findings of the study. The risk of non-response bias was high in all studies. While all studies had specific inclusion criteria to select participants that were reflective of the intended population, the extent to which the results could be extrapolated to national populations was unclear, as the studies were conducted at either a single site, or small number of sites across a large geographical area. The use of non-validated tools and lack of clear definitions of pain in most studies may introduce a degree of measurement bias.

While there is limited published evidence surrounding the assessment of pain and dyspnoea in acute exacerbations of COPD using standardised assessment tools, this may not be representative of how these symptoms are considered in frontline clinical care. Exploration of the practices of a patient's care team in assessing these symptoms during acute exacerbations of COPD opens an avenue for further research in this area. The impact of pain and dyspnoea on other clinical indicators such as hospital length of stay, and time to recovery from exacerbations of COPD require further exploration to understand the implications of these symptoms in this clinical state.

Within this review, the pooled prevalence of pain and dyspnoea in acute exacerbations of COPD was 44% and 91% respectively. Different outcomes measures were applied for pain and dyspnoea and the focal periods for assessment were defined by the assessment tool used. Despite the findings of this review demonstrating that pain and dyspnoea are experienced by a considerable proportion of people at the time of an acute exacerbation of COPD, the reporting of clinical associations and implications of both symptoms in this clinical state is minimal. In the treatment of an exacerbation of COPD, the management of pain is likely to be a lower clinical priority than correcting the underlying pathophysiological problems associated with the exacerbations. A greater understanding into the prevalence, intensity and associations of pain during exacerbations could be furthered by use of standardised assessment tools and clearly defined focal periods to capture the nature of pain and dyspnoea over the course of an exacerbation.

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) received no financial support for the research, authorship, and/or publication of this article.

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Appendix 1

MEDLINE search strategy

P	COPD	COPD	1
	COAD	COAD	2
	Chronic obstructive pulmonary disease	Chronic AND obstructive AND pulmonary AND disease	3
	Chronic AND obstructive AND airway(s) disease	Chronic AND obstructive AND airway$ AND disease	4
	Chronic bronchitis	Chronic AND bronchitis	5
	Emphysema	Emphysema	6
	Search 7: 1 OR 2 OR 3 OR 4 OR 5 OR 6		
P	Acute	Acute	8
	Exacerbation Exacerbated	Exacerbat$	9
	Flare-up	Flare-up	10
	Search 11: 8 OR 9 OR 10		
	Search 12: 7 AND 11		
O	Pain Painful	Pain$	13
O	Dyspnoea Dyspnea	Dyspn$	14
	Breathlessness Breathless	Breathles$	15
	Search 16: 14 OR 15		
	Search 17: 12 AND 13 AND 16		
1	COPD.mp		
2	COAD.mp		
3	(Chronic AND obstructive AND pulmonary AND disease).mp		

(continued)

Appendix 1 (continued)

P	COPD	COPD	I
4	(Chronic AND obstructive AND airway$ AND disease).mp		
5	(Chronic AND bronchitis).mp		
6	Emphysema.mp		
7	1 OR 2 OR 3 OR 4 OR 5 OR 6		
8	acute.mp		
9	exacerbate$.mp		
10	Flare-up.mp		
11	8 OR 9 OR 10		
12	7 AND 11		
13	pain$.mp		
14	dyspn$.mp		
15	breathles$.mp		
16	14 OR 15		
17	12 AND 13 AND 16		