Episodic Breathlessness in Patients With Advanced Disease: A Systematic Review

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Introduction

Breathlessness is one of the most common and distressing symptoms in advanced diseases, not only for patients but also for carers.[1] The American Thoracic Society (ATS) defines breathlessness as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses."[2] This consensus statement does not distinguish between different patterns of breathlessness, such as continuous breathlessness or episodic breathlessness (EB).

Patients describe breathlessness in relation to time, which can be characterized as continuous breathlessness (breathless all the time), episodes on the background of continuous breathlessness, and EB only (without breathlessness before and after the episode).[3] In the literature, various other terms are used for "episodes/episodic." Some more recent studies in cancer patients describe attacks of breathlessness.[1,4–7] Other terms are acute, breakthrough, incident, crisis, and intermittent.[7–11] In patients with chronic obstructive pulmonary disease (COPD), EB is mainly related to the acute exacerbation of the disease.[11]

Despite several advances in its management,[12,13] breathlessness remains difficult to treat successfully.[14] Therefore, a more in-depth understanding of breathlessness and especially EB with regard to characteristics and patients' experiences is necessary to provide better and more individualized treatment options to patients. The combination of acute and constant components of one symptom reminds us of the concept of breakthrough pain, with short exacerbations on top of baseline pain.[15] Although there are still inconsistencies in the use of the term "breakthrough pain," more work has been conducted in this area and specific recommendations exist for the management of breakthrough pain.[15] A similar way forward is postulated for the understanding and definition of episodic or breakthrough breathlessness.

As a first step, we systematically reviewed the literature to identify, critically appraise, and synthesize the evidence on EB regarding definition, characteristics, and patients' experiences of EB in advanced disease.

Methods

This systematic review follows the recommendations of the PRISMA statement.[16]

Definition of EB

As there is no official definition of EB, we use the following preliminary definition: "an increase in breathlessness occurring intermittently in patients with or without underlying continuous breathlessness." Other terms for "episodes/episodic" are acute, breakthrough, incident, crisis, attack, intermittent, spontaneous, and exacerbation.

Literature Search

We searched the following databases to the second week of March 2011: MEDLINE (from 1950), Embase (from 1980), PsycINFO (from 1806), British Nursing Index (from 1985) (all via Ovid), CINAHL (from 1981, via Ebscohost), and the Cochrane Library (Wiley Interscience). The search strategy used a combination of key words, medical subject headings (MeSH, exploded), and title- or abstract-free text words: "episodic" and "dyspnoea" were combined with terms for different diseases (lung neoplasm, COPD, chronic heart failure [CHF], motor neuron disease [MND], and interstitial lung disease [ILD]). The search was supplemented by searching the reference lists of included and relevant studies and using citation tracking in Ovid, PubMed, and Scopus. Authors were contacted for further studies and unpublished data. The following journals were hand searched from their first issue to March 2011: *Palliative Medicine*, *Social Science & Medicine*, *Chest*, and *Heart & Lung*.

Inclusion Criteria

Patients suffering from breathlessness as a result of advanced COPD, CHF, lung cancer, MND, or ILD were included. The advanced stage was defined as follows: COPD Stages III/IV, Global Initiative for Obstructive Lung Disease classification;[17] CHF Stages III/IV, New York Heart Association classification;[18] all stages

of lung cancer (primary or secondary lung cancer); MND; and ILD. As it was expected that reporting of the stage of disease might vary in the studies, studies also were included where patients were described as advanced or palliative with incurable disease or a limited prognosis, even if the criteria defined above (i.e., Global Initiative for Obstructive Lung Disease or New York Heart Association stage) were not used.

Selection Criteria

We included original research in English and published as full-text articles (no conference abstracts). As pilot searches suggested that EB is not commonly described in the literature, all study designs were included to ensure inclusion of all available published evidence. Studies were included if they described the symptom as EB, acute breathlessness, or an attack of breathlessness and reported specific information on 1) definition, categorization, and terminology; 2) characteristics of episodes in terms of frequency (number of episodes per day/week), duration (onset to maximum severity and to end), timing, intensity/severity, and concurrent symptoms; or 3) patients' experiences of EB in terms of individual descriptions of EB, triggers and trajectory of episodes, impact on daily living, individual coping strategies, and the perspective of informal carers. Any study that named the symptom but failed to provide information about characteristics or experiences was excluded. Dyspnea on exertion as a form of EB was included because it meets the definition of EB, given previously.

Studies of patients with asthma or other potentially curable diseases or exacerbations of a chronic disease (e.g., decompensation of CHF or acute exacerbations of COPD) were excluded, as these conditions are potentially reversible and do not describe the day-to-day experience of breathlessness of patients.

Data Collection and Analysis

Three reviewers (S. T. S., C. R., and E. S.) independently assessed titles, abstracts, and full texts. Data extraction with a standardized form was done by one reviewer (C. R.) and checked by S. T. S. Disagreement at any stage was resolved after discussion with a fourth reviewer (C. B.). Methodological quality was scored independently (S. T. S. and C. R.) using the National Institute for Clinical Excellence grading system,[19] the Edwards Method Score for intervention and nonintervention studies,[20] and the grading scale for qualitative and mixed-methods studies by Hawker et al.[21] The National Institute for Clinical Excellence grading system classifies study designs according to grade of evidence in a standardized way. Studies are classified into the following categories: Grade I (randomized controlled trial [RCT] or RCT review), Grade II (prospective study with a comparison group [e.g., non-RCT and good observational study] or retrospective study that controls effectively for confounding variables), and Grade III (retrospective or observational or cross-sectional studies).[19] The checklist of Edwards et al.[20] for methodological quality contains 11 items that assess the primary research quality of the studies using scores between 0 and 2 (e.g., definition of aims, description of inclusion and exclusion criteria, adequacy of analysis, intention to treat, and randomization method). Hawker et al.[21] present a checklist using nine questions to assess the methodological quality of qualitative and mixed-method studies (e.g., Sampling: Was the sampling strategy appropriate to address the aims?). Use of three assessment scales was necessary because of the inclusion of different study designs. Results were integrated in a narrative synthesis.

Results

The stages of the review process are summarized in the PRISMA flowchart (Fig. 1). Twenty-seven articles from 7585 references were included in this review.

Characteristics of Included Studies

Studies included patients of different disease groups (COPD,[1,8,11,22–25] lung cancer,[1,4–7,9,26] ILD,[27,28] and CHF[27,28]). No studies investigating EB in MND patients were identified. There was considerable heterogeneity in study designs and data collection methods. Overall, the methodological quality of studies was low to moderate (Table 1).

Definition, Categorization, and Terminology of EB

There was no general definition or terminology for EB. A definition for the term EB was

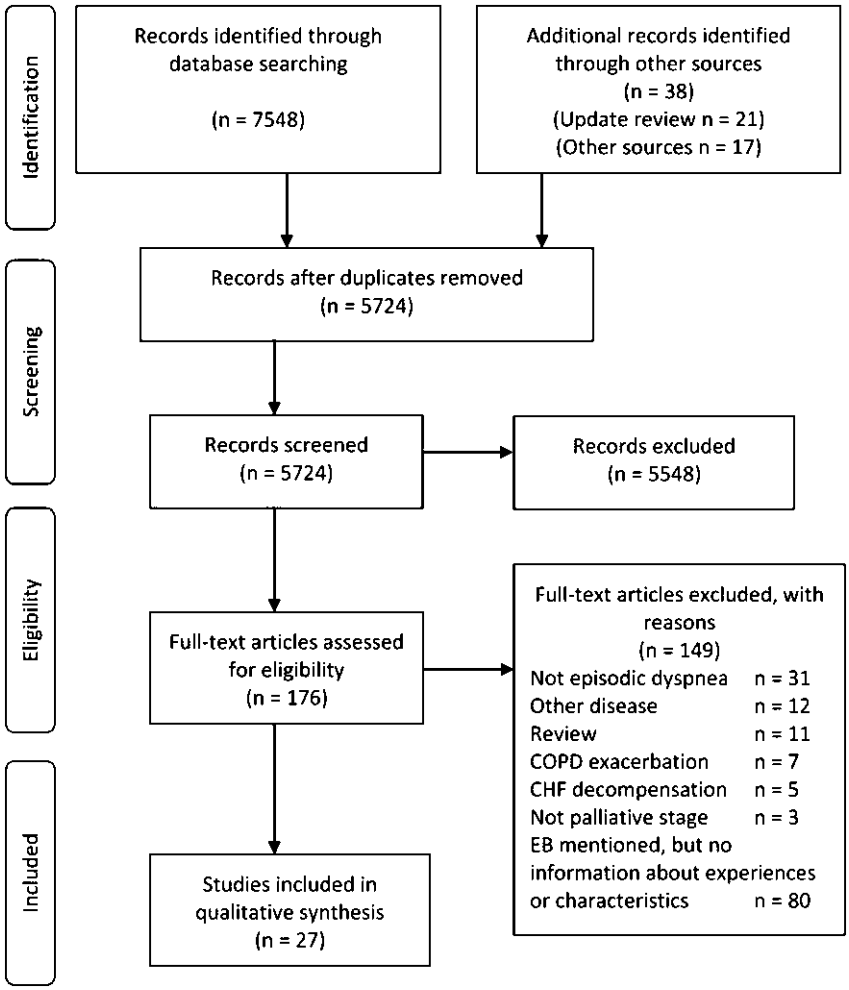

Fig. 1. Flow of information through the review.

only given in five studies. Reddy et al.[3] specified the term as "a clinically significant aggravation of dyspnea in patients with continuous dyspnea or occurring intermittently." Besides this content-based definition, Navigante et al.[9,10] and Charles et al.[29] used an event-based definition. Here, breakthrough dyspnea was described as episodes that required rescue medication. Similarly, in a study by Bailey,[11] EB was characterized as an acute event or episode that sometimes led to hospitalization. Most studies used the term without giving a definition or just using the general definition of dyspnea agreed on by the ATS.[2] A multitude of terms were used for EB. The most common terms were EB,[28,30] episodes of dyspnea,[1,4,7,8,11,23,24,26,27,29,31,32] acute dyspnea/breathlessness,[8,11] dyspnea on exertion/exertional dyspnea (activity-related dyspnea),[6,33] (severe) attacks of dyspnea,[4,7,22,25,33,34] escalating breathlessness,[35] intermittent breathlessness,[7] incident dyspnea,[9,29] or breakthrough dyspnea.[3,9,10] Often, more than one term for EB was used in a study.

There was no general categorization of EB, but authors used different categories to group EB:

1. EB is classified either as 1) dyspnea on exertion over a background of dyspnea at rest or as 2) a stand-alone symptom.[3,6,33,35,36]
2. EB is classified according to its triggering factors[4–7,11,24,25,31,33,35] (Table 2). In a qualitative study with 20 patients with advanced lung cancer and 12 hospitalized COPD patients, Henoch et al.[5] classified triggers into 1) physical (exertion), 2) psychosocial (personal characteristics, state of mind, excitement, expectation

Table 1

Study Characteristics (Ordered by Study Design)

First Author, Reference, Year, and Country	Design	Aim	Participants and Setting	Stage	Sample Size	Age and Gender (Mean [range])	NICE Score (Edwards/Hawker Score[a])
Aamodt,[22] 1988, Norway	RCT Crossover, double blind	To determine the efficacy of theophylline after continuous long-term treatment in adult patients	COPD Outpatients	Stable COPD with mean FEV_1 2.03 L (0.59–3.59 L), all patients on continuous corticosteroid therapy	21	48.1 (22–65) 9 m/12 f	IB 12/22
Charles,[29] 2008, Australia	RCT Crossover, double blind	To compare the efficacy of a nebulized opioid, a systemic opioid, and nebulized saline to provide rapid relief for incident dyspnea in patients with advanced cancer	56% lung cancer, 44% lung metastases Hospice (in- and outpatient)	Advanced disease, prognosis of at least seven days to live	20	69 (48–83) 11 m/9 f	IC 12/22
Navigante,[9] 2010, Argentina	RCT Parallel, single blind	To determine whether cancer dyspnea could be pharmacologically controlled while its underlying cause is sought or treated and which drug, morphine or midazolam, would be more suitable in this setting	30% lung cancer or lung metastases of sample with mixed cancer diagnoses Outpatients	Advanced, incurable patients	63	Midazolam: median 59 (36–82); morphine: 55 (30–80) Gender not reported	IB 16/22
Navigante,[10] 2006, Argentina	RCT Parallel, single blind	To assess the role of midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception during the last week of life in patients with advanced cancer	Sample with mixed cancers, 29.7% lung cancer Inpatients	Terminal	101	57.3 (—) 47 m/54 f	IB 12/22

(*Continued*)

Table 1
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First Author, Reference, Year, and Country	Design	Aim	Participants and Setting	Stage	Sample Size	Age and Gender (Mean [range])	NICE Score (Edwards/Hawker Score[a])
Fraticelli,[36] 1996, Italy	Prospective, observational study	To outline the main clinical, instrumental, and cognitive characteristics of aged subjects who are discharged from hospital with a diagnosis of CHF and evaluate the patterns of treatment of CHF in this elderly sample	CHF Inpatients	68% NYHA class III or IV (52% NYHA class III and 16% NYHA class IV)	50	76.6 (SD = 7.8) 35 m/25 f	IIIC 10/22
Michaels,[23] 2008, U.S.	Prospective, observational study	To examine rate of word use on low, moderate, and high breathing intensity days, relationship between rates of word use and psychosocial measures, and relationship between rates of word use and awareness of typical breathing and breathlessness	COPD Not reported	Moderate to severe, 50.22 FEV_1/FVC	45	70 (SD = 9) 62 m/2 f	IIIC 11/22
Reddy,[3] 2009, U.S.	Prospective, observational study	To characterize dyspnea, including differences between breakthrough and continuous presentations and determine factors correlated with the intensity of dyspnea	Mixed cancer, 44.3% lung cancer Inpatients and outpatients	Advanced, palliative patients	70	Median 58 (28–87) 40 m/30 f	IIIB 13/22

Escalante,[47] 1996, U.S.	Retrospective cohort study	To describe the patients presenting to an ED with dyspnea, determine the etiologies of dyspnea and the resource utilization associated with caring for these patients, and describe the one-year survival rate	Mixed cancer patients, 37% with lung cancer or lung metastases Inpatients	68% of sample had uncontrolled, progressive disease	122	Median 58 (29–90) 57 m/65 f	IIB 13/22
Henoch,[6] 2008, Sweden	Cross-sectional, retrospective	To describe and analyze the dimensionality of the dyspnea experience and examine the relations with other symptoms and personal and health-related factors in patients with lung cancer not amenable for further treatment with curative or life-prolonging intent	Lung cancer Inpatients	Palliative patients with metastatic disease	105	69 (36–85) 54 m/51 f	IIIB 10/22
Janson-Bjerklie,[24] 1986, U.S.	Cross-sectional, retrospective	To describe the sensation of dyspnea across pulmonary disease categories with specific focus on precipitants of dyspnea, prodromal indicators, physical and emotional sensations felt during the acute episode, and manifestations that could be observed by others	COPD,[24] five vascular, some of 13 with ILD Inpatients and outpatients	Moderate to severe, $FEV_1\% < 60\%$	68	54.3 (22–82) 29 m/39 f	IIIC 7/22

(*Continued*)

Table 1
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First Author, Reference, Year, and Country	Design	Aim	Participants and Setting	Stage	Sample Size	Age and Gender (Mean [range])	NICE Score (Edwards/Hawker Score[a])
Benitez-Rosario,[26] 2005, Spain	Case study	Four clinical cases in which oral transmucosal fentanyl citrate was effectively used in the control of dyspnea crises in terminally ill cancer patients	Lung cancer (one patient: lung metastases to colon cancer) Inpatients	All terminal, palliative patients	4	62 (52–72) 2 m/2 f	IIIC 5/22
Gauna,[27] 2008, U.S.	Case study	To evaluate the efficacy and safety of oral transmucosal fentanyl citrate in terminally ill patients experiencing dyspnea	COPD (two patients) Lung cancer (two patients with SCLC) Inpatients	All terminal patients (end-stage COPD and metastatic lung cancer)	4	68.75 (52–85) 2 m/2 f	IIIC 7/22
Sitte,[28] 2008, Germany	Case study	Three cases in which severe dyspnea was treated with intranasal fentanyl in patients receiving palliative home care	Lung cancer, CHF (+COPD), ILD + CHF Outpatients	All terminal palliative patients (metastatic disease, NYHA IV, progressive disease)	3	77.6 (72–88) 2 m/1 f	IIIC 3/22
Lomborg,[35] 2005, Denmark	Mixed-methods study	1) How patients with COPD perceive personal body care, 2) what is it like to be assisted in a hospital setting and with dyspnea, and 3) how patients manage the performance of assisted body care	COPD Inpatients	Severe COPD, hospitalized	12	68.5 (55–76) 5 m/7 f	IIIC 35/36
Thomas,[37] 2009, U.S.	Mixed-methods study	To identify dyspnea management strategies perceived most effective by elders with end-stage COPD	COPD Outpatients	GOLD II–IV, GOLD III and IV, 80% of sample, FEV_1 mean 38.2%	30	71.6 (57–86) 12 m/18 f	IIIC 25/36

Bailey,[11] 2004, Canada	Qualitative interview study	To explore further the affective component of dyspnea (anxiety), as described by patients and family caregivers living with an individual with COPD who has experienced acute exacerbations characterized by uncontrollable dyspnea	COPD Inpatients	Not reported, patients included with AECOPD who had had at least two previous AECOPDs	10	Not reported Not reported	IIIC 30/36
Barnett,[25] 2005, U.K.	Qualitative interview study	To explore the experiences of living with COPD	COPD Outpatients	Moderate-to-severe COPD patients recruited from a chest clinic	10	Not reported Not reported	IIIC 32/36
Booth,[1] 2003, U.K.	Qualitative interview study	To investigate and document the effects of breathlessness on the everyday lives of patients with cancer and COPD and their carers	Mixed sample of 10 COPD and 10 cancer patients (of which six had primary or secondary lung cancer) Outpatients	Not reported, but only patients who were breathless at rest (MRC dyspnea scale score of 3 or 4) were included	10	COPD: 70 (51–80) Cancer: 63.5 (51–77) 12 m/8 f	IIIC 34/36
DeVito,[31] 1990, U.S.	Qualitative interview study	How does the patient with COPD perceive the experience of dyspnea and nursing actions while hospitalized?	COPD Inpatients	Chronic bronchitis or emphysema who had been hospitalized at least once with AECOPD	96	Not reported Not reported	IIIC 29/36
Ek,[34] 2008, Sweden	Qualitative interview study	To describe the essential structure of the lived experience of living with severe COPD during the palliative phase of the illness	COPD Outpatients	All in palliative phase, all on home oxygen	8	–(48–79) 3 m/5 f	IIIC 30/36
Fraser,[32] 2006, U.S.	Qualitative interview study	To explore the experiences of older adults with severe COPD, how the disease had affected their lives	COPD Outpatients	All very severe COPD (GOLD), almost all oxygen dependent	10	71 (59–86) 5 m/5 f	IIIC 26/36

(*Continued*)

Table 1
Continued

First Author, Reference, Year, and Country	Design	Aim	Participants and Setting	Stage	Sample Size	Age and Gender (Mean [range])	NICE Score (Edwards/Hawker Score[a])
Gullick,[33] 2008, Australia	Qualitative interview study	To explore the changes experienced by a person living with COPD	15 COPD patients and 14 informal caregivers Outpatients	All patients with severe COPD, indicated by FEV_1% predicted range from 14% to 51%	29	COPD patients: median 63 (55–77) 9 m/6 f	IIIC 33/36
Gysels,[30] 2008, U.K.	Qualitative interview study	To explore the reasons for the disparity between the high needs and the low service use typically reported for breathless patients with COPD and their carers and what the dynamics are between patients and services that are responsible for the barriers experienced in accessing services	10 COPD patients and eight informal caregivers In- and outpatients	Moderate to severe (GOLD)	18	–(52–78) 7 m/11 f	IIIC 35/36
Henoch,[5] 2008, Sweden	Qualitative interview study	To describe lung cancer patients' experiences of dyspnea and their strategies for managing the symptom	Lung cancer, 14 NSCLCs and six SCLCs Inpatients	Advanced, 11 patients with metastases, no curative treatment	20	68.5 (56–79) 11 m/9 f	IIIC 33/36
Heinzer,[8] 2003, U.S.	Qualitative interview study	To describe the perceptions of dyspnea in hospitalized patients with COPD who experienced acute dyspneic episodes during the course of their inpatient stays, identify	COPD Inpatients	Not reported, patients hospitalized with AECOPD	41	70 (43–89) 26 m/15 f	IIIC 26/36

		COPD patients' needs, and assess the value given to current nursing care					
Lai,[4] 2007, China	Qualitative interview study	To determine perceptions of dyspnea in terminal lung cancer patients in a palliative care unit: 1) how patients describe dyspnea in their own words, 2) the impact of dyspnea on their illness, and 3) how they manage episodes of dyspnea	Lung cancer, seven NSCLCs and four SCLCs Inpatients	Terminal, Stages IIIB–IV	11	65.5 (54–75) 8 m/3 f	IIIC 31/36
O'Driscoll,[7] 1999, U.K.	Qualitative study, content analysis of handwritten assessment notes	To offer descriptive material regarding the experience of breathlessness in lung cancer (part of a study that developed and evaluated a rehabilitative intervention for dyspnea)	Lung cancer, 32 (62%) with NSCLC, 13 (25%) with SCLC, four mesothelioma, and three suspected lung cancer Outpatients	Not reported	52	60 (33–76) 30 m/22 f	IIIC 26/36

NICE = National Institute for Health and Clinical Excellence; RCT = randomized controlled trial; COPD = chronic obstructive pulmonary disease; f = female; m = male; FEV_1 = forced expiratory volume in the first second; CHF = chronic heart failure; NYHA = New York Heart Association; FVC = forced vital capacity; ED = emergency department; ILD = interstitial lung disease; SCLC = small cell lung cancer; GOLD = Global Initiative for Chronic Obstructive Pulmonary Disease; AECOPD = acute exacerbation of COPD; MRC = Medical Research Council; FEV_1% predicted = forced expiratory volume in the first second in % predicted; NSCLC = non-small cell lung cancer.

[a]Edwards Method Score[20] used for assessment of methodological quality of quantitative studies and Hawker scale[21] used for assessment of qualitative studies.

of breathlessness, anxiety, and tension), and 3) environmental triggers (warm or cold weather and altitude). Janson Bjerklie et al.[24] classified triggers into two groups: 1) personal factors (exertion and emotions) and 2) situational factors (allergens and environment).

3. EB was triggered by a cause (exertion, emotion, etc.) or occurred without a known trigger.[1,4,25,30,32–34] In a study of 11 lung cancer patients, EB occurred spontaneously, and COPD patients also reported that EB could suddenly come up and then disappear without explanation.[4] Gysels and Higginson[30] found that breathlessness was experienced most often all of a sudden without a specific trigger. Factors that triggered EB are listed in Table 2.

Characteristics of EB

Characteristics of EB, that is, prevalence, length of episodes, and severity/intensity of episodes, were mentioned in 13 studies[3,4,6–10,22,23,26,27,35,36] (Table 3). Only two studies described the prevalence of EB, with 81%–85% in patients with lung cancer.[3,7] Most patients experienced EB daily (around one to five episodes per day).[3,9,10,22,23,26] The length of EB was short, mainly about or less than five to 10 minutes,[3,4,7] and the intensity of breathlessness during EB was severe (with a mean of 7 on a 0–10 numerical rating scale).[8,26,27]

Patients' Experiences of EB, Impact on Daily Living, and Coping Strategies

No qualitative study was identified that explicitly explored EB. Experiences and descriptors of EB were extracted from articles that studied breathlessness in general and described EB as a special subgroup of breathlessness.

Seven studies (three in COPD patients)[4,5,7,8,11,31,37] reported on specific descriptors for EB, such as a heavy feeling in the chest, chest tightness, the inability to get air into the body (in lung cancer),[5,7] and hard to move air or labored breathing (in COPD).[4,7,8,11,24,31,37] A prodromal phase to EB, usually characterized by physical sensations, symptoms, or emotions, was recognized and generated a sense of awareness for the approaching episode.[11,24] Symptoms, such as pain, cough, and fatigue, accompanied EB.[3–7,11,24]

The impact of EB on daily living was multidimensional in terms of physical, psychosocial, social, and existential impact. The physical limitations caused by EB were described to affect quality of life.[1,4,5,34] Emotional reactions during EB, ranging from death fear to guilt, were regularly noted.[1,3–7,10,11,24] EB was

Table 2
List of Triggers

A1. Exertional/Physical Triggers	A2. Emotional Triggers	A3. Environmental Triggers
• Physical strain of any kind[5,7,11] • Exertion of any kind[1,7,25] • Rapid or excessive movement: bed making, moving furniture, walking fast or walking uphill/upstairs, dressing rapidly, and hurrying[4–7,24] • Nondemanding activities: walking short distances and being sedentary[5–7,24] • Activities directly involving the oral tract: talking, eating, and drinking[4,5,7,24] • Carrying heavy objects[7,24] • Activities of daily living: washing oneself, drying oneself, dressing, doing laundry, housework, shopping, and ironing[7,24,25] • Changing positions: bending and standing up[7,24] • Abdominal distensions[24] • Turning in bed[35] • Coughing[24]	• Crying[7] • Laughing[7,24] • Fear[7] • Anxiety[5,7,24,31] • Worry[24] • Anger and frustration[7] • Being emotionally upset[4,24] • Excitement[5,7,24] • Cognitive factors, expectation of dyspnea[5] • Tension[5,24] • Emotional distress, anxiety-dyspnea-anxiety cycle[11] • Acute arousal[24]	• Smoking (active or passive)[5,24] • Warm, cold, and combination of warm and cold weather[6,25,33] • Combination of cold and windy weather[6,7] • Extreme weather[4,7] • Altitude[5,24] • Allergens[24] • Awareness of improper breathing[5] • Hunger[4] • Lack of energy and wrong nutrition[4] • Fatigue[24] • Feeling too warm[24] • Alcohol[24] • Infections[24]

Table 3
Frequency, Length, and Severity (Ordered by Author)

Study (First Author, Reference, Year, Disease Group, Study Design)	Prevalence	Frequency of EB	Length of EB	Severity of EB (Measurement Tool)
Aamodt,[22] 1988, COPD, RCT ($n = 21$)	—	Number of nocturnal attacks: on theophylline before placebo, mean 3.0 (SD = 1); off theophylline, 4.4 (SD = 1.3); and on theophylline after placebo 2.3 (SD = 0.8)	—	—
Benitez-Rosario,[26] 2005, lung cancer, case study ($n = 40$)	—	Patient 1: seven episodes in 48 hours Patient 2: three episodes in one week Patient 3: two episodes in one week Patient 4: one episode in one day	—	Patient 1: episode 7/10 Patient 2: episode 5/10 Patient 3: episode 7/10 (Mod. Borg scale)
Fraticelli,[36] 1996, CHF, prospective observational study ($n = 50$)	43 of 50 (86%)	—	—	—
Gauna,[27] 2008, COPD and lung cancer, case study ($n = 4$)	—	—	—	Patient 1: episodes 7/10 and 8/10 Patient 2: episodes 8/10, 8/10, and 9/10 Patient 3: 6/10 and 8/10 Patient 4: 7/10 and 7/10 Average severity of dyspnea: 7.5/10
Heinzer,[8] 2003, COPD, qualitative study ($n = 41$)	—	—	—	Mean 7 (range 3–10) (Mod. Borg Scale)
Henoch,[6] 2008, lung cancer, cross-sectional study ($n = 105$)	—	Not at all: 49 (46.7%) Less than once a week: 7 (6.7%) Some time every week: 12 (11.4%), Some time every day: 31(29.5) All the time: 6 (5.7%)	—	Dyspnea on walking: not at all 27 (25.7%), a little 48 (45.7%), quite a bit 22 (21%), very much 5 (4.8%), missing 3 (3%); Dyspnea when climbing stairs: not at all 21 (20%), a little 39 (37.1%), quite a bit 26 (24.8%), very much 18 (17.1%), missing 1 (1%) (EORTC QLQ-LC13)
Lai,[4] 2007, lung cancer, qualitative study ($n = 11$)	—	Most severe dyspnea attack occurred more than 20 times a day in one patient	Commonly lasted from five to more than 10 minutes, duration varied	—
Lomborg,[35] 2005, COPD, mixed-methods study ($n = 12$)	—	—	—	After exertion: mean 4.5 (range 0.5–9) (Mod. Borg Scale)
Michaels,[23] 2008, COPD, observational ($n = 45$)	—	Episodes per day: mean 5.5 (SD = 5.2)	—	—
Navigante,[9] 2010, mixed cancer, RCT ($n = 63$)	—	Day 1: mean 1.9 episodes (Mo group), 1.9 (Mi group) Day 2: 1.3 (Mo), 0.8 (Mi) Day 3: 1.6 (Mo), 0.8 (Mi) Day 4: 1.8 (Mo), 0.9 (Mi) Day 5: 1.9 (Mo), 0.4 (Mi)	—	—

(*Continued*)

Table 3
Continued

Study (First Author, Reference, Year, Disease Group, Study Design)	Prevalence	Frequency of EB	Length of EB	Severity of EB (Measurement Tool)
Navigante,[10] 2006, mixed cancer, RCT ($n = 101$)	—	Baseline: median number of episodes 2 (Mo group) 1 (Mi group) 1 (Mo + Mi)	—	—
O'Driscoll,[7] 1999, lung cancer, qualitative study ($n = 52$)	44 of 52 (85%)	—	Attacks: minutes to hour; most common duration: five to 15 minutes	—
Reddy,[3] 2009, mixed cancer, observational study ($n = 70$)	57 of 70 (81%)	One to five episodes per day: 55% Six or more episodes per day: 13% Unknown: 13%	≤1 minute: 26% Two to 10 minutes: 61% ≥11 minutes: 9% Unknown: 3%	—

EB = episodic breathlessness; COPD = chronic obstructive pulmonary disease; RCT = randomized controlled trial; Mod. Borg Scale = Modified Borg Scale; CHF = chronic heart failure; EORTC QLQ-LC13 = European Association for the Research and Treatment of Cancer Quality of Life Questionnaire lung cancer module; Mo = morphine; Mi = midazolam.

perceived as a crisis.[8,11,31,32,35] Reddy et al.[3] found that constant dyspnea with EB demonstrated a higher interference with function in all aspects as compared with EB only.

The coping strategies of patients can be categorized into physical, psychological, and pharmacological (Table 4).[5,37] Most patients used nonpharmacological strategies, and several studies mentioned that patients adopted their own strategies of what works during an episode by trial and error.[4,7,24]

Discussion

This is the first systematic review assessing all available evidence about the characteristics and experiences of EB. Although we identified 27 studies, overall information on EB is scarce. Only eight studies explored EB as a primary objective, and all other data were extracted from studies about breathlessness in general in which patients described EB. In summary, EB is described as a short period of severe breathlessness that occurs mainly daily and impairs patients' quality of life by limiting activity and causing panic and fear.

Lack of Definition for EB

One important finding is that a general and agreed definition for EB is lacking. This precludes comparisons and is a barrier for further research. The definition of breathlessness by the ATS in 1999 is widely accepted and used, but EB is mentioned only once in this statement, in connection with insufficient treatment options for EB.[2] A specific definition of EB is not provided. Our literature review identified only five studies that defined EB. Four of those used an event-based approach, defining EB as breathlessness that requires rescue medication or hospital admission.[9–11,29] Only one study defined EB more in depth as a clinical aggravation of dyspnea.[3] The presented definitions are mainly opinions of individual authors or groups but they are based neither on patient data nor on a consensus of a wider group of experts. A consensus statement about dyspnea crisis was mentioned within a conference abstract (no full text), but the consensus project concentrates on management rather than characteristics and patients' experiences of EB.[38] In addition, different terms for EB

Table 4
List of Management Strategies

Physical Strategies	Psychological Strategies	Other Strategies
• Get fresh air[37] • Keep still[7,35,37] • Move slower, pacing[4,35,37] • Avoiding bodily exertion and triggers[4,5,7] • Stop or modify activity to conserve energy[37] • Sit down[37] • Relaxation[5,7,37] • Pursed lip breathing, deep slow breathing, active breathing exercises, and positioning[4,5,7,32,37] • Drinking warm or cold water[4] • Sitting up[7]	• Plan in advance[5,35,37] • Cognitive: repression, explaining away, ignoring, enduring, distracting, accepting, and protecting[1,5] • Concentration[5] • Good family support[4] • Asking for help[7] • Taking advice from loved ones or health care professionals only helpful during severe episodes[32] • Struggling to not let go/fighting[35] • Coping with dependency[35]	• Oxygen[4,5,32,37] • Inhalers[4,32,37] • Use help of health care professionals[5] • Traditional Chinese medicines[4] • Acupuncture[4] • Movement of fresh air[7] • Fans[7] • Steam inhalations[7]

are used at the moment. Consensus about the definition and terminology is urgently needed to foster further development and research in this area—similar to the consensus about breakthrough pain.[15,39] Because of the multidimensionality of the symptom, a consensus definition should best be developed on the basis of patients' experiences and an expert consensus process.

Characteristics of EB and Clinical Implications

EB can be characterized as being short in duration (in most cases, less than 10 minutes), quite severe (on average 7/10 on a numerical rating scale), and occurring in most patients daily (often one to five times a day). This seems to be similar to breakthrough pain, which occurs on average three to four times a day with moderate or severe intensity and a median duration of 30–60 minutes but with a huge variation of 1–480 minutes.[40,41] However, the duration of breathlessness episodes is described to be much shorter.[3,4,7] Although further confirmation of the characteristics in larger populations and different disease groups (especially other than lung cancer or COPD) is needed, these characteristics of EB might have important implications for clinical practice. First, immediate-release morphine is widely used as rescue medication for EB, with an onset of action of 30–60 minutes.[42] This seems to be inappropriate for EB because of the short duration of the symptom. Second, opioids with a faster onset and shorter duration, such as fentanyl,[27,43] might be more promising for the treatment of EB, but no controlled studies have been published yet. Third, it could be questioned whether pharmacological interventions are appropriate at all to relieve EB. There is a plurality of patients' self-management strategies, and psychological strategies are used most often.[4,5,7,32,35,37] Because of the limitations of pharmacological options, nonpharmacological strategies might be the best way to date to prevent and relieve EB. However, this needs further exploration. Recent progress in the development and evaluation of comprehensive breathlessness services with a focus on optimization of treatment and self-management is promising and might lead to better support of patients with EB.[44,45]

Impact on Patients

The impact of breathlessness in general on patients' and carers' lives has been described widely,[46] but as studies normally do not distinguish between breathlessness in general, constant breathlessness, and EB, it is not clear what type has the biggest impact. Only one study compared patients with constant breathlessness and those with EB showing that patients with constant breathlessness have more limitations in exercise capacity compared with patients with EB only.[3] This requires further exploration.

Strengths and Weaknesses

This systematic review, for the first time, distinguishes different types of breathlessness and explores EB in more detail across conditions.

The literature was searched broadly, and the selection process of potential studies included three independent reviewers. There are also some weaknesses. First, because of the lack of an agreed definition of EB, we could have missed studies that did not meet our preliminary definition. However, we chose a broad approach including all different types of definitions (including breathlessness on exertion) and terms for EB to get a comprehensive picture of this symptom. Second, for most included studies, EB was not the primary outcome, and information needed to be extracted from studies that evaluated mainly breathlessness in general. We chose a conservative approach for the extraction and included information only if it was explicitly related to EB. Therefore, we could have missed additional data that might be related to EB but are not clearly described as such. Third, our search strategy was limited on the symptom of EB. We did not search for specific causes of EB, thus we did not include search terms, such as "exercise," "exertional," or "acute exacerbation." In addition, we did not include diagnostic procedures to differentiate various causes of EB, such as X-ray, lung function, or blood tests in the data extraction, because the aim of the study was to explore the definition, characteristics, and patients' experiences of EB.

Conclusion

EB is a common symptom in patients with advanced diseases that causes distress in patients and carers and impairs quality of life. Based on studies in patients with lung cancer, COPD, and CHF, EB can be characterized as short in duration (often less than 10 minutes) and with high severity. It occurs often daily. These characteristics are challenging for its management (e.g., onset of action of drugs is often longer than duration of EB). Therefore, to date, nonpharmacological strategies might be best to treat this symptom effectively and enhance quality of life, but further exploration is needed. EB is underresearched in MND and ILD. Although it is a common symptom in advanced disease, information about its characteristics is still scarce, and it is only rarely recognized as a distinct entity of dyspnea. A consensus about the definition and terminology of EB is needed to enable better comparisons of studies and foster research in this area.

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