Original Article

Epidemiology and Characteristics of Episodic Breathlessness in Advanced Cancer Patients: An Observational Study

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Abstract

Context. Episodic breathlessness is a relevant aspect in patients with advanced cancer.

Objectives. The aim of this study was to assess the different aspects of this clinical phenomenon.

Methods. A consecutive sample of patients with advanced cancer admitted to different settings for a period of six months was surveyed. The presence of background breathlessness and episodic breathlessness, their intensity (numerical scale 0–10), and drugs used for treatment were collected. Factors inducing episodic breathlessness and its influence on daily activities were investigated.

Results. Of 921 patients, 29.3% ($n = 269$) had breathlessness and 134 patients (49.8%) were receiving drugs for background breathlessness. In the multivariate analysis, the risk of breathlessness increased with chronic obstructive pulmonary disease, although it decreased in patients receiving disease-oriented therapy and patients with gastrointestinal tumors. The prevalence of episodic breathlessness was 70.9% ($n = 188$), and its mean intensity was 7.1 (SD 1.6). The mean duration of untreated episodic breathlessness was 19.9 minutes (SD 35.3); 41% of these patients were receiving drugs for episodic breathlessness. The majority of episodic breathlessness events (88.2%) were triggered by activity. In the multivariate analysis, higher Karnofsky Performance Status levels were significantly related to episodic breathlessness, although patients receiving disease-oriented therapy were less likely to have episodic breathlessness.

Conclusion. This study showed that episodic breathlessness frequently occurs in patients with breathlessness in the advanced stage of disease, has a severe intensity, and is characterized by rapid onset and short duration, which require rapid measures. J Pain Symptom Manage 2016;51:17–24.

Key Words

Episodic breathlessness, dyspnea, advanced cancer, palliative care, opioids

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Introduction

Breathlessness is defined as a subjective experience of breathing discomfort, commonly known as dyspnea, which consists of qualitatively distinct sensations that vary in intensity.[1] In the last days of life, breathlessness often becomes more severe and refractory to traditional medical management. Breathlessness is a disabling and distressing symptom reported by patients with advanced cancer, particularly in the last three months of life and in patients with lung cancer,[2] although it occurs in 46% of all cancer outpatients.[3] Breathlessness is associated with significant suffering both for patients and their caregivers. This symptom is the most common chief complaint for admission to hospital in patients with lung cancer.[4]

Breathlessness is a multifactorial problem generated through different modalities and pathways, requiring complex and multiple interventions according to the specific individual situation and the clinical context. It may be caused by cancer itself, and preexisting or concomitant comorbid conditions.[5] This symptom may resemble the characteristics of pain according to some temporal characteristics. Although breathlessness may be a continuous phenomenon present for most hours of the day, clearly distinguishable episodes of intensified breathlessness may overlap the background condition (episodic breathlessness). As breathlessness is a complex entity difficult to manage, it is of paramount importance to gather data about this phenomenon to optimize treatment and provide better and individualized therapeutic options.

The aim of this observational prospective study was to assess the prevalence of breathlessness and episodic breathlessness, their characteristics, and possible factors implicated in their development in patients with advanced cancer. The secondary aim was to assess common treatments in a large number of patients.

Patients and Methods

A consecutive sample of patients with advanced cancer admitted to seven different centers, which included oncology, home care, palliative care unit, or hospice settings, during a period of six months (April 2014 to September 2014) was prospectively assessed for this survey. All patients able to provide information about breathlessness were eligible, and no patient was excluded a priori.

Informed consent and institutional approval from the University of Palermo were obtained. At the time of admission, the epidemiological characteristics, stage of disease, concomitant comorbidities, and oncologic treatments were recorded. A specific form was designed and filled in during the initial assessment visit. The researcher asked about the presence of breathlessness, its intensity on a numerical scale from 0 to 10 (where 0 = none and 10 = worst imaginable) over the past 24 hours, and drugs used for its treatment, as part of the assessment. Patients also were asked if they had episodic breathlessness that was well distinguished from background breathlessness over the past 24 hours; possible factors associated with episodic breathlessness; and if it influenced daily activities or specific positions. Given the multicenter nature of the study, a standardized definition for episodic breathlessness (after agreement of the Home Care Italy [HOCAI] study group) was used: "a predictable or unpredictable increase in breathlessness occurring intermittently, clearly distinguishable in intensity from continuous breathlessness, if present." When episodic breathlessness occurred, intensity (on a numerical scale from 0 to 10 [where 0 = none and 10 = worst imaginable]) and duration were recorded. Finally, patients were asked if they were receiving drugs for relieving such episodes.

Statistical Analysis

According to previous studies, at least 900 patients were necessary to gather data for more than 150 patients with episodic breathlessness. The statistical analysis, to assess an association pattern between breathlessness and clinical comorbidities, was carried out by chi-square tests of statistical association, with a confidence level of 5%. No correction for Type I error was provided at this level because of its explorative intent. Afterward, a logistic regression with outcome variables, breathlessness, and episodic breathlessness was performed adjusting for age and gender, providing the odds ratios of clinical and statistical importance. Model fitting was assessed by a likelihood ratio test at a 5% Type I error level. Descriptive statistics of the variables considered are provided. The analysis was done with STATA version 13 (StataCorp LP, College Station, TX).

Results

A total of 921 patients were surveyed. The mean age was 70.3 (SD 12.7) years, and 445 patients were male. The primary tumors were, in a rank order, as follows: lung 206 (22.6%), gastrointestinal 304 (33.4%), breast 94 (10.3%), hematological 83 (9.1%), urological 57 (6.2%), gynecological 51 (5.6%), brain 42 (4.6%), prostate 35 (3.8%), head and neck 20 (2.2%), others 19 (2.1%), and unavailable data 10 (1%). Four hundred seventeen patients (45.3%) were receiving disease-oriented therapy, including chemotherapy, hormonal therapy, or targeted therapy.

Breathlessness

The prevalence of breathlessness was 29.3% ($n = 269$). In these patients, the mean intensity of breathlessness was 4.2 (SD 1.9). One hundred thirty-four patients (49.8%) were receiving drugs for background breathlessness. The categories of drugs are listed in Table 1.

Associated comorbidities were, in a rank order, as follows: cardiovascular disease (41.1%), chronic obstructive pulmonary disease (COPD) (14%), renal failure (9.3%), liver dysfunction (2.7%), and others (12.4%). Breathlessness was significantly associated with age, cancer diagnosis, and disease-oriented therapy (Table 2). In the multivariate analysis, the risk of breathlessness increased with COPD, whereas it decreased in patients receiving disease-oriented therapy and patients with gastrointestinal tumors (Table 3).

Episodic Breathlessness

The prevalence of episodic breathlessness was 70.9% ($n = 188$), and its mean intensity was 7.1 (SD 1.6). The mean duration of untreated episodic breathlessness was 19.9 minutes (SD 35.3). Of the 188 patients, 78 (41%) were receiving one or more drugs for episodic breathlessness (Table 4).

The majority of episodic breathlessness events were triggered by activity, including going upstairs (12.2%), walking (20.2%), recumbency (6.4%), change of position (9.6%), going upstairs and walking (26.3%), and all (13.3%). In 11.8% of cases, no precipitant factors were found.

In 133 patients (70.4%), episodic breathlessness interfered with daily activities: going upstairs 12.3%, walking 29.4%, recumbency 6.4%, change of position 9.7%, going upstairs and walking 26.3%, and all 15.6%.

Episodic breathlessness was significantly associated with cancer diagnosis and Karnofsky Performance Status (Table 5). In the multivariate analysis, higher Karnofsky levels were significantly related to episodic breathlessness, although patients receiving disease-oriented therapy were less likely to have episodic breathlessness (Table 6).

Discussion

This study provides epidemiological data and characterization of episodic breathlessness in a large sample of patients with advanced cancer, half of them receiving disease-oriented therapy. About one-third of patients (29.3%) had breathlessness with significant intensity, and half were receiving a background treatment, principally based on corticosteroids. Most of these patients had other health conditions. Of this sample, a significant number of patients (70.9%) had episodic breathlessness of severe intensity clearly distinguishable from background breathlessness, which lasted about 20 minutes and primarily induced by activity.

Table 1
Lists of Drugs Used for Breathlessness (in Some Cases, Multiple Treatments)

Corticosteroids	85 (31.6%)
Opioids	46 (17.1%)
Benzodiazepines	8 (3%)
Bronchodilators	47 (17.5%)
Oxygen	41 (15.2%)

Table 2
Frequency of Breathlessness (BLN) According to the Variables Taken Into Consideration

Variable	BLN	No BLN	*P*-value
Age			
≤65 yrs	96 (36.2%)	208 (33.7%)	
>65 yrs	169 (67.7%)	437 (63.7%)	0.14
Gender			
Male	126 (46.84%)	318 (48.8%)	0.75
Female	143 (53.16%)	332 (51.2%)	
Cancer			
Lung	114 (43%)	92 (14.2%)	0.0000
Breast	20 (7.5%)	73 (11.4%)	
Gynecological	11 (4.1%)	40 (6.3%)	
Urological	13 (4.9%)	44 (6.9%)	
Gastrointestinal	53 (20%)	250 (39.1%)	
Hematological	27 (10.2%)	55 (8.6%)	
Brain	8 (3%)	31 (4.8%)	
Prostate	8 (3%)	27 (4.2%)	
Head-neck	7 (2.6%)	13 (2%)	
Others	4 (1.5%)	15 (2.3%)	
Comorbidity			
CVD	117 (43.5%)	257 (40.2%)	0.4
COPD	67 (25.3%)	59 (9.3%)	0.0000
Kidney disease	27 (10.1%)	57 (8.9%)	0.6
Liver disease	7 (2.6%)	18 (2.8%)	0.9
Karnofsky			
≤40	170 (63.2%)	384 (59.6%)	
50–60	66 (24.5%)	169 (26.2%)	
≥70	33 (12.3%)	91 (14.1%)	0.0000
Treatment			
Disease-oriented	109 (26.2%)	306 (73.5%)	
Palliative care	156 (31.2%)	339 (67.9%)	0.11

CVD = cardiovascular disease; COPD = chronic obstructive pulmunary disease.

Prevalence

The prevalence of breathlessness in advanced cancer patients has been reported to be variable, depending on the setting and stage of disease.[3,6] In this sample of patients with advanced cancer, we found a breathlessness prevalence of about 30%, with a consistent intensity, 4/10 on average. Different from pain, in which some cutoff points to differentiate mild, moderate, and severe intensity have been established, for breathlessness, no specific studies have assessed how much mild or moderate breathlessness is considered to influence most daily activities.[7]

Existing data regarding episodic breathlessness in the literature are sparse, despite a growing interest in the last years. The definition used in this

Table 3
Multivariate Analysis for Breathlessness

Breathlessness	Odds Ratio	$P > \|z\|$	95% CI	
Age	0.9772248	0.001	0.9637212	0.9909176
Gender	0.7009879	0.055	0.4876736	1.007609
Karnofsky	0.9950524	0.381	0.9840645	1.006163
Disease-oriented therapy	0.6398776	0.011	0.4540057	0.9018464
CVD	1.13644	0.456	0.8117733	1.590956
COPD	3.248147	0.000	2.098814	5.026866
Kidney disease	0.9534902	0.870	0.5398021	1.684216
Liver disease	0.7857181	0.646	0.2805056	2.200858
Lung	1.99209	0.173	0.7396618	5.365184
Gastrointestinal	0.3424446	0.036	0.1259366	0.931169
Urological	0.4482893	0.173	0.1412815	1.422432
Breast	0.3805674	0.089	0.1250216	1.158452
Hematological	0.9817316	0.973	0.3362079	2.86667
Gynecological	0.3707008	0.106	0.1111446	1.236399
Prostate	0.5881789	0.407	0.1676311	2.063784
Brain	0.5076033	0.267	0.1532334	1.681495
Others	0.5028533	0.373	0.1108688	2.280726
Head-neck	Omitted because of collinearity			

CVD = cardiovascular disease; COPD = chronic obstructive pulmunary disease. $P = 0.0000$.

study resembles previous operational definitions.[8,9] Episodic breathlessness also has been considered as incident dyspnea on a background of either irreversible dyspnea at rest or when speaking, in patients using a stable regular dose of an opioid,[10] assuming that the treatment should be reserved to opioid-tolerant patients.

Controversies exist in the literature about the relationship and coexistence of breathlessness and episodic breathlessness. In a qualitative study, 51 patients suffering from breathlessness from COPD, lung cancer, and motor neuron disease were interviewed. Patients described a clear relationship between breathlessness and episodic breathlessness.[11] At the same time, 22% of interviewed patients had episodic breathlessness only, without background breathlessness. It is likely that the long duration assigned for episodic breathlessness (less than 24 hours) was not clearly distinguishable from breathlessness (longer than 24 hours), providing an uncertain space, called out-of-the-blue,[8] which was able to confound these findings. On the other hand, the mean duration of episodic breathlessness (see the following) has been reported to be short, within 10 minutes.[12] This observation should limit the definition of episodic breathlessness for episodes with a shorter duration.

In a clinical study of advanced cancer patients with dyspnea, 80% of patients experienced episodic breathlessness. However, despite the predefined definition (aggravation of breathlessness …), episodic breathlessness was recorded alone in 61% of patients, suggesting that it often occurs without background breathlessness.[9] But, a number of patients with constant breathlessness did not report episodic breathlessness. It is likely that a misinterpretation of the questionnaire may have biased the results, as confirmed by the higher intensity of constant breathlessness in comparison with episodic breathlessness. Moreover, most patients with obvious causes of breathlessness were excluded.[9] In a mixed population, episodes of breathlessness were more severe and longer in patients with COPD than in those with lung cancer; in cancer patients, 90% presented with more than three episodes a day.[13]

Duration and Intensity

Although a real cutoff duration has never been defined, it is likely that the temporal pattern should circumscribe patients having episodic breathlessness with a duration up to minutes–hours; otherwise, it could be defined as continuous breathlessness, persisting for many hours of the day. For a similar temporal phenomenon, breakthrough pain, most episodes last less than one hour.[14,15] Duration and intensity are the most particular characteristics that may help in providing a clear distinction with normal oscillations in symptom intensity during the day. This also has a relevant meaning in terms of therapeutic interventions. In this study, the mean duration of episodic breathlessness was about 20 minutes. In previous patient-reported experiences described in the literature, the most frequent duration of episodic breathlessness was 5–15 minutes.[9,13,16,17] Of concern, a risk of recall bias cannot be excluded.

Table 4
Drugs Use to Relieve Episodic Breathlessness

Oxycodone	16 (20.5%)
Morphine	46 (59%)
Fentanyl mucosal products	4 (5.1%)
Benzodiazepines	5 (6.4%)
Bronchodilators	13 (16.7%)
Corticosteroids	17 (21.8%)

Table 5
Frequency of Episodic Breathlessness (EBLN) According to the Variables Taken Into Consideration

Variable	EBLN	No EBLN	*P*-value
Age			
≤65 yrs	65 (34.2%)	27 (38.6%)	
>65 years	125 (65.8%)	43 (61.4%)	0.55
Gender			
Male	90 (47.9%)	32 (45.7%)	
Female	98 (52.1%)	38 (54.3%)	0.83
Cancer			
Lung	75 (40.5%)	34 (48.6%)	0.03
Breast	20 (10.8%)	0	
Gynecological	8 (4.3%)	4 (4.3%)	
Urological	9 (4.9)	2 (2.9%)	
Gastrointestinal	34 (18.4%)	17 (24.3%)	
Hematological	22 (11.9%)	5 (7.1%)	
Brain	3 (1.6%)	4 (5.7%)	
Prostate	7 (3.8%)	1 (1.4%)	
Head-neck	4 (2.2%)	3 (4.3%)	
Others	3 (1.6%)	1 (1.4%)	
Comorbidity			
CVD	87 (46.3%)	25 (35.7%)	0.3
COPD	51 (27.6%)	14 (20.3%)	0.15
Kidney disease	18 (9.6%)	8 (11.4%)	0.86
Liver disease	4 (2.1%)	3 (4.3%)	0.6
Karnofsky			
≤30−40	113 (60.1%)	51 (72.8%)	
50−60	45 (23.9%)	16 (22.9%)	
≥70	30 (16%)	3 (4.3%)	0.035
Treatment			
Disease oriented	76 (72.4%)	29 (27.6%)	
Palliative care	112 (71.8%)	44 (28.2%)	0.26

CVD = cardiovascular disease; COPD = chronic obstructive pulmunary disease.

In this study, which provided a clear definition of episodic breathlessness, the intensity of episodic breathlessness was higher (about 7/10) in comparison with values of breathlessness (about 4/10); this helps confirm the clear distinction in the definition of episodic breathlessness, which is different from common oscillations throughout the day, and resembles recent observations on breakthrough pain.[18] This aspect has been recently assessed in an expert consensus where episodic breathlessness was considered as a high-intensity episode distinguished from usual fluctuations of breathlessness.[8] On other occasions, overlapping intensities of breathlessness and episodic breathlessness were confounding factors.[8,9] In the literature, the mean number of episodic breathlessness occurrences has been reported to be one to five per day.[12] We did not assess this number, as we expected that it was strongly dependent on the will or the need to start an activity or not, as occurs with breakthrough pain with an incident component because of movement.

Factors Inducing Episodic Breathlessness

Episodic breathlessness can be triggered (or not) by identifiable factors, in particular by increasing physical activity. Other triggers have been identified, including emotional or environmental factors. In an interview-based report of patients with different diseases, about half of patients did not report any warning before an episode.[8] In this study, almost all episodes were predictable and triggered by activity. Raw measurements at time of admission, patient selection, and a clear definition may explain the differences found in this study.

As for breathlessness,[6] psychological factors often have been reported as a possible cause of episodic breathlessness.[11] However, it is likely that the relationship could be inverse, and episodic breathlessness contributes to the development of anxiety and depression, for its obvious influence on the psychological sphere, although a vicious cycle with somatization cannot be excluded.[9]

The interference of episodic breathlessness with activities confirmed previous data.[9] It is likely that

Table 6
Episodic Breathlessness Multivariate Analysis

Episodic Breathlessness	Odds Ratio	$P > \|z\|$	95% CI	
Age	0.9986193	0.925	0.9704388	1.027618
Gender	1.086376	0.797	0.5783075	2.04080
Karnofsky	1.043001	0.000	1.018839	1.067736
Disease-oriented therapy	0.4561336	0.041	0.2145301	0.9698305
CVD	1.814815	0.084	0.9237964	3.565237
COPD	1.829534	0.128	0.8404821	3.982468
Kidney disease	0.4824401	0.167	0.1717012	1.355543
Liver disease	0.3415434	0.243	0.0563634	2.069638
Lung	1.229628	0.807	0.2347424	6.441036
Gastrointestinal	0.8152178	0.818	0.1434317	4.633424
Urological	3.976354	0.235	0.4083309	38.72201
Breast	Omitted because of collinearity			
Hematological	2.609311	0.328	0.3817814	17.83351
Gynecological	1.584504	0.682	0.1748755	14.3568
Prostate	3.051325	0.417	0.2057638	45.24888
Brain	0.1991798	0.175	0.0193269	2.052713
Others	0.502853 3	0.373	0.1108688	2.280726
Head-neck	Omitted because of collinearity			

CVD = cardiovascular disease; COPD = chronic obstructive pulmunary disease.

episodic breathlessness may occur as a result of extreme fatigue triggered by emotional, environmental, or physical triggers. Fatigue is very common symptom in advanced cancer patients and has been reported to be correlated with high-intensity breathlessness.[6,9] Meaningfully, fatigue may have a prominent role, independent from a pulmonary problem.[19] Therefore, indirectly, patients with fatigue may limit or prevent episodic breathlessness by reducing their level of activity. Interestingly, exercise has been used as a model for inducing episodic breathlessness.[20] It could be surprising that episodic breathlessness is more likely in patients with higher Karnofsky Performance Status scores. Paradoxically, patients with a higher Karnofsky score are more physically active and, therefore, more likely to experience episodes of breathlessness on exertion. These data are consistent with the information reported for breakthrough pain in oncology patients and those with far advanced cancer followed at home.[21,22]

Cancer Diagnosis and Comorbidities

COPD had been found to be strongly associated with background breathlessness, but not to episodic breathlessness.[17] It is likely that other factors, not included in this analysis, may have flattened these data. Fatigue could induce episodic breathlessness when an activity is requested. Interestingly, patients receiving disease-oriented therapy were less likely to have episodic breathlessness. This aspect, as for pain, is an interesting issue and deserves further study to gather information about the relationship between an oncology treatment and symptom intensity.

Treatment of Breathlessness and Episodic Breathlessness

Recent articles have focused their attention on episodic breathlessness, suggesting some parallels with the treatment of breakthrough pain. The temporal characteristics and duration of episodic breathlessness suggest a rapid intervention, independent from the treatment of background breathlessness. Breakthrough pain is an exacerbation of pain intensity on a well-controlled background pain, generally treated by opioids.[14,15] However, different from background pain intensity, it is quite difficult to define an "acceptable" background breathlessness. Unlike chronic pain, breathlessness poses therapeutic challenges, as drugs commonly used have an indirect effect and there are no specific first-choice treatments.

In this study, corticosteroids were found to be the drugs most frequently administered, with opioids being used in a minority of patients. Of interest, the administration of these drugs was focused on breathlessness, although the use for other purposes cannot be excluded, as frequently it occurs in palliative care. Despite these treatments, the mean level of breathlessness was 4/10, corresponding to a moderate intensity. It would be interesting to establish the level of patients' acceptability of these levels of breathlessness, as occurs for background pain, and whether an optimization of background treatment, for example, with opioids, could be helpful; also, in increasing the tolerability of effort, thus reducing the occurrence of episodic breathlessness. It has been suggested that opioid-naïve patients could be slowly titrated because inadequate dosing may generate no response.[23]

In this study, 40% of patients with episodic breathlessness were receiving a pharmacological treatment for it, and about 80% of them were receiving oral opioids. Oral opioids do not fit the temporal characteristics of episodic breathlessness, as their effect starts about 30 minutes after administration.[24] In a controlled trial of patients receiving regular opioids, fixed doses of inhaled hydromorphone produced an improvement in episodic breathlessness 20 minutes after starting nebulization, although this effect was not observed with systemic administration or placebo.[10] It is remarkable that opioids were given for episodic breathlessness to opioid-tolerant patients in fixed doses.

Fentanyl products have been "borrowed" from breakthrough pain management for the treatment of episodic breathlessness. This approach has been suggested by the similar temporal characteristics of these two phenomena. It is remarkable to note that transmucosal fentanyl preparations are given to opioid-tolerant patients for controlling background pain,[24] although patients with breathlessness often do not receive opioids chronically. This issue poses problems of dosing fentanyl for episodic breathlessness. It is reasonable that lower doses of fentanyl could be titrated against the effect in opioid-naïve patients, and higher doses would be necessary for opioids-tolerant patients receiving opioids for chronic pain or dyspnea. In another trial, doses of parenteral fentanyl given prophylactically, proportional to opioids given chronically (15−25%), were safe and effective.[20] This study suggests that fentanyl products could be given before an expected trigger, as it is for preventing predictable breakthrough pain, for example, before starting an activity.

Most case series provide promising effects.[12] A randomized controlled study demonstrated an improvement in exercise tolerance after fixed doses of inhaled fentanyl in comparison with placebo.[25] However, this study was performed in noncancer patients with pulmonary disease. Given the short onset and duration of episodic breathlessness, it is likely that fentanyl products with the fastest effect would be preferred. Although some relief 15 minutes after transmucosal administration of fentanyl[26] has been

reported, a placebo effect was observed in a controlled study,[27] possibly as a result of the slower onset of action in comparison with new generations of fentanyl delivery systems providing a clinical meaningful effect within 5–15 minutes. Moreover, a patient with fatigue experiencing episodic breathlessness is not fit enough to rub the stick in the mouth. Of interest, other fentanyl delivery systems are easier to use and do not need specific patient participation.

This study had some limitations. First, the risk of recall bias cannot be excluded in breathlessness evaluation. The finding of no emotional triggers for breathlessness may be related to the way in which the question was framed, and nonpharmacological approaches were not consequently assessed. The prescription of some symptomatic drugs could be associated with other clinical indications. Finally, the role of fatigue was not assessed and could have a determinant role in triggering the episodes.

In conclusion, data gathered from this study suggest that episodic breathlessness frequently occurs in patients with breathlessness in the advanced stage of disease, has a severe intensity, and is characterized by rapid onset and short duration that require rapid measures. These results should be interpreted with caution, given the preliminary and observational nature of the study. The generalizability of study results should be confirmed in subclasses of patients with different stages of disease, Karnofsky level, primary diagnosis, comorbidities, and setting of care in a larger number of patients. The influence of other symptoms, such as fatigue, should be explored. Future research should establish which level of background breathlessness is acceptable for patients, as occurs with chronic pain, and whether dose optimization of background opioids given for breathlessness, balancing antidyspneic effects and adverse effects, may be useful in preventing or limiting the occurrence of episodic breathlessness. Moreover, dosing of fentanyl products for episodic breathlessness should be better investigated according to the level of tolerance provided by background opioids given for breathlessness or pain.

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