



# Outcome measurement of refractory breathlessness: endpoints and important differences

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## Purpose of review

Standardized measurement of self-rated breathlessness using appropriate tools is essential for research and clinical care. The purpose was to review recent advances in the measurement of breathlessness and the minimal clinically important differences (MCIDs) in intensity of chronic breathlessness.

## Recent findings

Two tools have been validated in people with chronic obstructive pulmonary disease (COPD) to measure daily symptoms and breathlessness related to daily activities. Two multidimensional tools have been developed for different settings and aetiologies, which measure both the perceived intensity, unpleasantness, quality of breathlessness, and the person's emotional response to it. MCIDs have been reported for the intensity of chronic refractory breathlessness, the daily symptom diary, and breathlessness related to daily activities in COPD.

## Summary

There have been substantial developments in instruments able to provide reliable and valid unidimensional and multidimensional measurement of self-reported breathlessness and in the understanding of the MCID for chronic breathlessness. Routine use of agreed outcome measures in clinical practice and research are crucial steps to improve our understanding of the science of breathlessness and its impact on patients' outcomes.

## Keywords

breathlessness, dyspnea, minimal clinically important difference, outcome measure

## INTRODUCTION

Breathlessness is the subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity [1]. A useful model identifies multiple dimensions of this symptom that can be differentiated by the individual: the experienced intensity and unpleasantness, the associated emotional response, and the functional impact on the person's life [1]. Breathlessness, which persists despite optimal medical management of underlying disease(s), is termed to be refractory [2]. Refractory breathlessness is common in advanced illness, increasing in prevalence as death approaches across a range of underlying diseases [3<sup>••</sup>]. It is associated with limited physical activity, deconditioning, increased anxiety and depression, impaired quality of life, loss of the will to live near death, increased risk of hospitalization, and earlier death [1,4<sup>•</sup>].

The importance of breathlessness has been highlighted in recent years. For instance, breathlessness

has been included in the evaluation of disease severity [5<sup>•</sup>] and is a good measure for determining prognosis in chronic obstructive pulmonary disease (COPD) [5<sup>•</sup>].

Despite the high prevalence and its serious impact, breathlessness remains frequently underreported, unmeasured, and undertreated in clinical

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## KEY POINTS

- Several tools for measuring breathlessness have been developed to comply with regulatory requirements for valid endpoints in randomized trials.
- Unidimensional tools include measures of severity breathlessness in daily life and related to daily activities in COPD.
- Multidimensional tools include the dyspnea-12 and the MDP.
- The MCID has been determined for ratings of chronic refractory breathlessness, severity in daily life, and breathlessness related to daily activities.

practice [6<sup>\*</sup>]. Standardized measurement is essential to identify the presence and quantify the severity of breathlessness, to initiate evidence-based management and demonstrate effectiveness of services [7]. The level of breathlessness should be reassessed routinely in the clinic to evaluate the patient's response, risk for adverse events, and need for follow-up and further treatment [7].

As breathlessness is a subjective sensation, measurement should be by self-report unless this is not possible, in which case proxy measures should be sought [1,7]. There is currently no consensus of or gold standard for which measurement tools to use [1,8–10]. Tools can be categorized as unidimensional, measuring one aspect of breathlessness, for example, visual analogue scale (VAS) or numeric rating scale (NRS) for intensity or unpleasantness, the Borg scale for exertion induced intensity, or the modified Medical Research Council Dyspnea (mMRC) for impact on function [1]. Tools that measure several aspects of breathlessness are called multidimensional and include the Cancer Dyspnoea Scale (CDS) and the Chronic Respiratory Disease Questionnaire (CRQ) [9–11].

Parallel to the importance of measuring breathlessness in clinical practice, there has been a growing interest in measures of breathlessness as endpoints in randomized controlled trials (RCTs) [1,8–10,12<sup>\*</sup>]. Measures need to meet scientific and regulatory validation criteria [13<sup>\*\*</sup>].

The minimal clinically important difference (MCID) is a fundamental concept when evaluating change or effect of treatment both in clinical trials and practice [12<sup>\*</sup>]. The MCID is defined as the smallest difference in score in the domain of interest, which patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient's management [14]. Recent years have seen

a rapid progress in the development of patient-reported outcomes, and the publication of several validated measurement tools of different aspects of breathlessness.

The aim of this article was to critically review recent advances regarding the measurement and clinically important difference of chronic breathlessness in people with advanced, life-limiting disease.

## Search strategy

We searched Medline up to January 29, 2015 using the search terms (dyspnea/dyspnea/breathlessness/shortness of breath/breathing difficult) OR (palliative care/palliative/palliation/terminal/advanced disease/severe disease) AND (measure/outcome/endpoint/clinically important difference/MID/MCID). Searches were restricted to adults and articles in English. Reference list of identified articles and personal libraries were searched, including for articles in press. The search covered the latest research captured over the last 3 years, as few papers were published in 2014. The selection criteria for inclusion in the review were that the article provided quantitative data on the measurement of self-reported breathlessness in severe or life-limiting disease.

## MEASUREMENT OF BREATHLESSNESS

Tools published in recent years (Table 1) include the unidimensional exacerbations of chronic pulmonary disease respiratory symptom (E-RS) diary of daily symptom severity (E-RS) [13<sup>\*\*</sup>] and a score of shortness of breath with daily activities (SOBDA) in COPD [15<sup>\*</sup>]. Multidimensional tools include the Dyspnea-12 questionnaire [16] and the Multidimensional Dyspnea Profile (MDP) [17–19<sup>\*\*</sup>]. The tools (Table 1) were all developed to comply with Food and Drug Administration regulatory requirements for valid endpoints in RCTs [13<sup>\*\*</sup>].

We also identified an article that examined the level of agreement between proxy assessment of breathlessness by healthcare professionals and patient self-report [20<sup>\*</sup>].

### Unidimensional tools of daily symptoms and breathlessness related to daily activities: exacerbations of chronic pulmonary disease respiratory symptom and shortness of breath with daily activities

E-RS is a diary of the severity of respiratory symptoms in stable COPD [13<sup>\*\*</sup>]. It consists of 11 items from a tool, which was originally developed for

**Table 1.** Included tools and MCIDs for breathlessness

Tools	Dimensions of breathlessness	Validation populations	Anchor-based MCID
Unidimensional			
ER-S	Intensity in daily life	Stable COPD outpatients	1 point
VAS	Intensity	Refractory chronic breathlessness (COPD, ILD, cancer, and heart failure)	9 mm (95% CI, 2.1 to 15.8)
SOBDA	Intensity related to daily activities	COPD outpatients	0.13–0.25 points
Multidimensional			
Dyspnea-12	Breathing discomfort, sensory qualities, and emotional responses, not related to activity	Asthma, COPD, ILD, and heart failure	No MCIDs reported
MDP	Breathing discomfort, sensory qualities, and emotional responses, not related to activity	Patient seeking an emergency department for acute breathlessness	No MCIDs reported

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; MCID, minimal clinically important difference; MDP, Multidimensional Dyspnea Profile; SOBDA, shortness of breath with daily activities; VAS, 100-mm visual analogue scale.

measuring symptoms during COPD exacerbations [21]. Items involve the presence and severity of symptoms ‘today,’ and relate to personal care, indoor, and outdoor activities. Content validity was explored through interviews with COPD patients. The diary was then validated in 188 patients with stable COPD [52% females; mean forced expiratory volume in 1 s (FEV<sub>1</sub>) 51% of predicted] over 7 days [13<sup>22</sup>]. Factor analysis showed that the diary measured three underlying constructs: breathlessness; cough and sputum; and chest symptoms (congestion, tightness and discomfort). The breathlessness domain (range 0–17 points with higher scores indicating more severe breathlessness) showed good reliability, test–retest reproducibility, and external validity as supported by a strong correlation with health-related quality of life, mMRC breathlessness score, FEV<sub>1</sub>, and rescue medication use.

Responsiveness over 3 months was shown using data from three prospective clinical trials [22<sup>23</sup>]. The E-RS is a validated diary to measure the severity of breathlessness as a summary score in daily life, for people with COPD.

Wilcox *et al.* validated the first questionnaire specifically for the measurement of SOBDA for use in both clinical trials and care of people with COPD [15<sup>24</sup>]. Questions were based on qualitative interviews and validated over 28 days in 334 COPD patients (48% females; mostly moderate to severe airflow limitation) recruited from medicine clinics in the USA. Using Rasch analysis, 13 items were found to measure breathlessness during daily activities and were included in the final SOBDA questionnaire [15<sup>24</sup>]. The mean weekly SOBDA score (range 1–4 with greater scores indicating higher activity-related breathlessness) was found to account for

daily variations in activity, had high reliability and validity, and was more informative than the mean daily score.

Responsiveness was shown over 6 weeks using data from a placebo-controlled RCT of inhaled glucocorticoid and/or bronchodilator in 336 COPD patients [23<sup>25</sup>]. The weekly mean SOBDA score is a reliable, valid, and responsive measure of breathlessness during daily activities in COPD [23<sup>25</sup>].

### Multidimensional tools: Dyspnea-12 and Multidimensional Dyspnea Profile

The Dyspnea-12 is a summary score of a person’s severity of breathlessness, which requires no reference to activity [16]. The score was developed using Rasch analysis and has been validated in patients with asthma, COPD, interstitial lung disease, and heart failure [16,24,25]. The Dyspnea-12 consists of 12 descriptor items rated on a 4-point Likert scale (none, mild, moderate, and severe) by recall of the severity of breathlessness ‘these days’ [16]. The overall score ranges between 0 and 36 with higher scores indicating worse breathlessness. The Dyspnea-12 has shown good test properties with high internal consistency, validity, and test-retest reliability over 2 weeks. The score captures several dimensions including intensity, unpleasantness, and emotional responses, as supported by strong correlations with measures of anxiety and depression, health-related quality of life, and mMRC breathlessness scale [16]. The Dyspnea-12 is short and relatively simple tool. It does not clearly separate the dimensions of breathlessness, and the recall of breathlessness ‘these days’ might limit its usefulness in relation to some settings, activities, or interventions. Dyspnea-12 is available in several languages and has been

validated in a range of cardiopulmonary diseases [16,24].

The MDP was developed to separately measure the immediate breathing discomfort, sensory qualities, and emotional responses irrespective of the underlying cause of breathlessness in both laboratory and clinical, including acute care, settings [17,18]. A revised version was recently published by Banzett *et al.* [19<sup>11</sup>] and can be used free of charge. The MDP consists of 11 rating scale items between 0 (minimum) and 10 (maximum), which are divided into two parts measuring separate constructs: the immediate perception of breathlessness and the emotional response. The first part includes a rating of the immediate breathing discomfort as well as the presence and intensity of five breathing qualities (breathing effort, air hunger, chest tightness, mental breathing effort, and breathing a lot). The second part consists of ratings of the intensity of five emotional responses: depression, anxiety, frustration, anger, and fright [19<sup>11</sup>]. The time frame or situation is defined by the user: ‘now,’ ‘over the past 24 hours,’ or ‘after this activity’ for example. The tool has been validated in response to laboratory stimuli [19<sup>11</sup>], and in a clinical study of 151 patients admitted to an emergency department (ED) for acute breathlessness (29% had asthma, 27% COPD, 19% pneumonia, 13% heart failure, 13% other) [17]. Recall ratings were reliable and responsive over hours during the ED visit supporting their usefulness. However, recall for items 4–6 weeks after the ED visit was less reliable [18]. In contrast to the multidimensional Dyspnea-12 and the CDS [11], MDP captures the immediate breathing discomfort, sensory qualities, and emotional responses separately during a user-defined period [19<sup>11</sup>]. It was developed based on previous research to enable translation between laboratory and clinical settings, across populations and diseases. MDP usually takes around 3 minutes to complete [19<sup>11</sup>]. To date, it is available in English and French [19<sup>11</sup>]. Validation in further settings is warranted.

### **Are professionals’ assessments of breathlessness valid?**

Although self-report by the patient is the gold standard for measures of breathlessness, this is sometimes not possible and clinical management will rely on proxy assessments. Proxy measures from informal carers are known to be useful [26,27].

Simon *et al.* [20<sup>12</sup>] measured the consistency between breathlessness assessment by healthcare professionals (80% physicians and 18% nurses) and self-report by 2623 inpatients in specialized palliative care. Almost all (96%) of patients had

cancer (15% lung cancer). Breathlessness was rated on a 4-point Likert scale (none, mild, moderate, and severe).

The level of agreement was good for the presence of any breathlessness but lower for rating severity. For the presence of any breathlessness (mild or higher), professionals’ reports had a positive predictive value of 82% and a negative predictive value of 79% [20<sup>12</sup>]. The severity of breathlessness was correctly estimated by professionals 66% of the time, with an even distribution of overestimations and under estimations. Agreement tended to be higher in people with better functional status as compared with people with more impaired function. Agreement did not differ between physicians and nurses. The good proxy identification of the presence of breathlessness might reflect the strong emphasis on symptom management in specialized palliative care. Proxy assessment of breathlessness may be less accurate in other professional disciplines [28].

## **CLINICALLY IMPORTANT DIFFERENCES**

### **Estimation**

The MCID can be estimated using distribution-based and anchor-based methods [12<sup>13</sup>].

The distribution-based method relies on the assumption that the average MCID corresponds to an effect size (change after intervention divided by standard deviation of baseline score) [29]. However, this method cannot determine whether this difference was perceived as clinically important by the patient, and it is recommended that it is used in conjunction with anchor-based methods [29].

Anchor-based methods estimate the MCID as the average difference in breathlessness in patients experiencing a small change in an anchor – another relevant and validated assessment tool, such as quality of life, another measure of breathlessness, activity, or a global impression of change [30<sup>14</sup>]. It is important that the anchor is at least moderately associated with the breathlessness score [12<sup>13</sup>]. More recently, patient preference has been used as an anchor, which encompasses net benefit [31<sup>15</sup>,32<sup>16</sup>]. Of note, an MCID estimate involves assumptions and uncertainties and reflects a group average; the true MCID for the individual might be higher or lower depending on a range of clinical factors and circumstances [12<sup>13</sup>].

### **Minimal clinically important difference of chronic refractory breathlessness intensity: visual analogue scale**

The MCID for chronic refractory breathlessness was estimated by Johnson *et al.* [31<sup>15</sup>] by pooling data



from three clinical trials of oral opioids vs. placebo [2,33,34], and one observational phase II/IV study of oral sustained-release morphine (n=85; 49% COPD, 28% cancer) for up to 3 months [35]. The anchor-based MCID was the difference in mean change of breathlessness between the preferred and the nonpreferred study arm, according to blinded self-reported treatment preference at the end of each 4-day treatment period [31<sup>11</sup>]. The intensity of breathlessness was measured using a 100-mm VAS in one study [2] and a 0–10 NRS in the other [33–35].

Distribution-based estimates were a mean 5.5-mm change for a small effect, 11.3 mm for moderate, and 18.2 mm for a large improvement [36]. The anchor-based MCID for improvement in chronic refractory breathlessness was 9 mm [95% confidence interval (CI), 2.1–15.8) on a 100-mm VAS. The MCID for chronic breathlessness was smaller than previous estimates for acute breathlessness in decompensated heart failure (22 mm) and acute asthma (21 mm) [37,38]. This might reflect that patients with chronic breathlessness, who often have adapted to and lived with their symptoms for many years, might appreciate even small changes in breathlessness in an important way. The MCID was consistent with a previous consensus [39] and distribution-based estimate [40].

Using the same pooled data, Johnson *et al.* evaluated whether it is best to report MCID of absolute or relative (percentage) change in chronic breathlessness. The estimated relative MCID was 14% (change from baseline), but showed marked variability at lower baseline breathlessness values. The absolute MCID was more stable across breathlessness intensities with the additional advantage that it can be calculated by both methods, whereas a relative MCID can be calculated by anchor-based methods only.

Taken together, this analysis is the largest to date and supports that studies of the intensity of chronic breathlessness should be powered to detect an absolute MCID of 9 mm on a 100-mm VAS or, correspondingly, 1 point on a 0–10 NRS and that this change equates to a moderate effect size [31<sup>11</sup>].

### **Minimal clinically important difference of severity of daily breathlessness: exacerbations of chronic pulmonary disease respiratory symptom**

The MCID for the E-RS breathlessness diary was estimated to 1.85 points using a distribution-based method [13<sup>11</sup>]. A second study suggested an anchor-based MCID of 1 point (scale range: 0–17) both for

improvement and worsening of breathlessness [22<sup>11</sup>]. Change was defined as a change above the MCID for the anchors St. George's Respiratory Questionnaire, a symptom questionnaire, and the 6-minute walk test [22<sup>11</sup>].

### **Minimal clinically important difference of breathlessness related to daily activities: shortness of breath with daily activities**

The MCID for SOBDA was between 0.14 and 0.21 points using a distribution-based method [15<sup>11</sup>]. Anchor-based MCID was consistent at between 0.13 and 0.25 points [15<sup>11</sup>,23<sup>11</sup>]. Anchors used to define change were patient global assessment of change and CRQ-SAS [23<sup>11</sup>].

### **Multidimensional tools: Dyspnea-12 and Multidimensional Dyspnea Profile**

We found no published data on the MCIDs for overall or component scores of the Dyspnea-12 or the MDP.

## **CONCLUSION**

There has been marked recent development in the measurement of breathlessness. Validated tools are now available for a symptom diary of daily life (E-RS) and the severity of breathlessness during daily activities in stable COPD (SOBDA), breathlessness not related to activity as a multidimensional summary score (Dyspnea-12), or measuring dimensions separately (MDP). MCIDs are available for the intensity of chronic refractory breathlessness on a VAS or NRS, E-RS, and SOBDA (Table 1). The MCID needs to be established for the multidimensional Dyspnea-12 and MDP instruments.

Structured measurements by self-report are imperative for identifying and treating breathlessness. The recent developments are likely to facilitate reliable and valid measurement of the dimensions of breathlessness across settings, populations, and etiologies in both research and for the individual patient in clinical care.

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**Conflicts of interest**

*There are no conflicts of interest.*

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