Original Article

Agreement Between Breathlessness Severity and Unpleasantness in People With Chronic Breathlessness: A Longitudinal Clinical Study

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Abstract

Context. Chronic breathlessness is a cardinal symptom in cardiopulmonary disease where both overall intensity or severity (S) and unpleasantness (U) are commonly quantified.

Objective. We aimed to evaluate agreement between breathlessness severity and unpleasantness over eight days in patients with chronic breathlessness.

Methods. Longitudinal analysis of 265 patients with chronic breathlessness who rated current overall breathlessness severity and unpleasantness on a 0−100 mm visual analogue scale (VAS) in the morning and evening over eight days. A total of 3630 paired overall severity-unpleasantness (S−U) differences were analyzed; median 15 (IQR 13−16) per patient. Agreement was evaluated using Bland-Altman plots. Associations of the difference between severity and unpleasantness (S−U difference) with clinical factors and perceived quality of life were analyzed using multilevel linear regression adjusted for confounders.

Results. Over eight days, severity and unpleasantness scores were highly correlated, had similar variability, and varied more between patients than within patients. The mean S−U difference was small at 2.1 mm. Agreement between overall severity and unpleasantness was similar or higher than expected from the variability in individual scores. The S−U difference was similar across evaluated factors including age, sex, diagnosis, morning/evening assessment, modified Medical Research Council breathlessness score, morphine treatment, and presence of different sensory qualities of breathlessness. Higher overall severity and unpleasantness associated with worse perceived quality of life in a similar way.

Conclusion. In patients with chronic breathlessness over eight days, overall severity and unpleasantness of breathlessness were comparable and associated to other clinical factors in a similar manner. J Pain Symptom Manage 2019;57:715−723.

Key Words

Dyspnea, COPD, cancer, ILD, quality of life, measurement, severity, unpleasantness

Introduction

Breathlessness, the "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity,"[1] is common in the community.[2,3] Chronic breathlessness was recently defined as "breathlessness that persists despite optimal treatment of the underlying pathophysiology and results in disability" including both breathlessness at rest and at limited exertion.[4] In people with severe disease,[5] this troubling symptom is associated with major adverse health outcomes.[6−9]

To date, there is no agreed standard for routine assessment of chronic breathlessness in clinical practice or minimum data set recommended for research

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endpoints.[10–12] A variety of instruments exist, which assess one or more distinct dimensions of the symptom: sensory quantity (intensity or severity), level of unpleasantness, sensory quality (descriptors of the sensation), emotional response, and impact on function.[1,13] Instruments exist for measuring multiple dimensions of breathlessness, for example, the Dyspnea-12 and the Multidimensional Dyspnea Profile (MDP).[14,15] The most commonly assessed dimensions of breathlessness are the overall intensity or severity and the overall unpleasantness, often measured using unidimensional scales such as a 0-10 numerical rating scale (NRS) and 0-100 mm visual analogue scale (VAS).[1,16]

Under controlled conditions, the intensity and unpleasantness of experimentally induced acute breathlessness can be differentiated both by people with and without chronic breathlessness.[17–19] During symptom-limited exercise tests, ratings of intensity and unpleasantness have been shown to have different trajectories, with unpleasantness increasing markedly as the subject draws near to his or her ventilatory capacity.[20,21] This suggests that the underlying perceptual mechanisms and potential behavioral importance may differ between overall breathlessness intensity and unpleasantness. Whether people living with chronic breathlessness can reliably differentiate between the overall severity and unpleasantness of breathlessness in everyday life is unknown.

In large populations or in people with more severe disease, assessment of several symptom dimensions may be less feasible and increase the rate of missing data.[22] In such studies, breathlessness is commonly assessed during daily life using a single measure of breathlessness—either as overall severity, or intensity, or unpleasantness.[23–26] Unidimensional scales (VAS or NRS) are commonly used to quantify the overall experience of intensity or severity of breathlessness[23–29] with various anchors (0—"no" and 10—"worst," "worst I can imagine," or "very severe"),[25,29] differing question stems ("How short of breath are you, "[How]" intense is your shortness of breath?"), and focal periods ("right now," "average/worst/peak over the past 24 hours").[24,25,29]

No published study has, to the authors' knowledge, evaluated the agreement between paired measurements of overall breathlessness severity and unpleasantness in a clinical cohort of patients with chronic breathlessness over time. It is unknown to what extent the dimensions are comparable for the individual and on the group level. The relationship between self-rated breathlessness severity and unpleasantness has important implications for comparison of outcomes between studies and for the choice of assessment tools in research and clinical care.

The aims of the present study were to evaluate the 1) variability and agreement of paired ratings of breathlessness severity and unpleasantness over eight days in patients living with chronic breathlessness; 2) clinical factors associated with the magnitude of difference between breathlessness severity and unpleasantness (S−U difference); and 3) associations of intensity, unpleasantness, and the S−U difference with worse perceived quality of life (QoL). First, we hypothesized that the ratings of breathlessness severity, unpleasantness, and the S−U difference would vary over time and between people living with chronic breathlessness. Second, that the S−U difference could be clinically important and contribute independent information in the individual, but that mean breathlessness severity and unpleasantness scores would be comparable at the group level.

Material and Methods

Design

This was a secondary analysis of a randomized, parallel arm, multisite, placebo-controlled, phase III trial of 20 mg extended release morphine daily compared with placebo in patients with chronic breathlessness (Australian New Zealand Clinical Trials Registry, ACTRN12609000806268).[30] The trial was approved by the Southern Adelaide Clinical Research Ethics Committee (Dnr: EC00188) and the local ethics committee at each site before the first recruitment at each site. All patients gave their informed written consent to participate, and the trial was monitored in accordance with Good Clinical Practice.[31]

Population

Participants were recruited from 14 respiratory and palliative care services across Australia in the Australian Government–funded national Palliative Care Clinical Studies Collaborative. Main inclusion criteria were as follows: age ≥ 18 years, chronic breathlessness defined as a modified Medical Research Council (mMRC)[32] breathlessness score ≥ 2 at the screening despite optimal management of underlying causes of breathlessness, stable breathlessness medications for the previous week except "as needed" medications, and expected survival ≥ 2 months. Main exclusion criteria were as follows: Australia-modified Karnofsky Performance Status (AKPS) scale score < 40,[33] treatment with ≥20 mg oral morphine equivalents per day the previous week, any contraindication for opioid treatment, and inability to give informed consent or complete a daily diary.

Assessments and Definitions

Data were collected at a baseline visit on age, sex, body mass index (BMI) calculated as measured weight (kg)/height $(m)^2$, mMRC breathlessness score,[34]

functional status (AKPS),[33] main chronic disease diagnosis, and multimorbidity using the Charlson Comorbidity Index (CCI) score.[35] Participants were also invited to select up to three descriptors at baseline, which best matched their sensations of breathlessness "now" from a list of 19 descriptors developed by Simon et al.[36] Data on descriptors were not obtained at some centers because of insufficient time for assessment or for patients who did not complete the form. Data on a single best matching descriptor were not available. To decrease the risk of bias due to ordering, each patient completed one of five sheets with the descriptors in different randomized orders. Descriptors were categorized in accordance with the MDP into five sensory qualities[15]: air hunger (smothering, suffocating, cannot get enough air, out of breath, hunger for more air, gasping for breath, cannot take a deep breath, or breath does not go in all the way), physical breathing effort (breathing requires more work or breathing requires effort), chest tightness (chest feels constricted or chest feels tight), hyperpnea (breathing is rapid, breathing more, or breathing is shallow), or mental breathing effort (breathing requires more concentration).

Participants completed a diary each morning and evening commencing the day before randomization (baseline) and for seven days of intervention (low-dose morphine or placebo), resulting in a potential maximum of 16 assessments across eight days. On each assessment, participants were asked to rate the overall severity and unpleasantness of breathlessness "now" on a 100-mm horizontal VAS. The VAS is a reliable and valid scale for unidimensional measurement of breathlessness.[1,37] Severity was assessed using the question "How is your breathlessness right now?" between 0 ("none") and 100 ("worst possible"). Unpleasantness was then assessed using the question "Right now how would you rate the unpleasantness of your breathlessness?" between 0 ("none") and 100 ("the most unpleasant I have ever felt"). Overall perceived QoL was assessed using the question "Considering all parts of your life—physical, emotional, social, spiritual, and financial—over the last 2 days, your quality of life was," rated on a 11-point NRS between 0 ("very bad") and 10 ("excellent") in each evening diary.

Statistical Analyses

Baseline characteristics were summarized with mean and standard deviation (SD) or with median and interquartile range (IQR) for continuous variables with normal or non-normal distributions, respectively. Categorical variables were expressed as frequencies and percentages.

All available severity and unpleasantness ratings were included in the analyses. The S−U difference, defined as the severity score minus its concurrent unpleasantness score, was calculated at morning and evening across eight days, yielding up to a maximum 16 S−U difference scores per participant. Time since baseline of each morning and evening assessment (12-hour steps) was used as a time scale in all analyses. Variability (SDs) within participants (over time) and between participants in the severity, unpleasantness, and S−U difference was calculated.

Agreement between severity and unpleasantness scores was evaluated by Bland-Altman plots. The systematic mean difference and 95% limits of agreement were calculated, accounting for repeated measurements in accordance with Bland and Altman.[38] Agreement was evaluated across the whole assessment period and at each of the 16 assessment points. As the level of agreement between severity and unpleasantness possible to obtain was limited by the underlying variability of the separate scores,[39] we assessed whether the observed agreement was less than expected from the variability in the scores. To this end, the limits of agreement were compared with the variability of the severity and unpleasantness scores expressed as their repeatability coefficients (2.77 × SD within participants for each score).[39]

Associations between clinical factors and the magnitude of S−U difference were evaluated using multilevel linear mixed-effects regression. The model accounted for repeated measurements within patients and allowed participants to differ in the mean breathlessness level (random intercepts) and change over time (random slopes). Available clinical factors of interest based on the literature included age, sex, mMRC score at baseline, time of assessment (12-h steps) since baseline, whether the score was a morning or evening assessment, treatment arm (morphine vs. placebo), BMI, AKPS, QoL, primary underlying chronic disease diagnosis (chronic obstructive pulmonary disease [COPD] vs. other), multimorbidity (CCI score), and presence of sensory qualities of breathlessness.[1,3] The estimates of the final multivariable model were robust when compared with models using stepwise (forward and backward) variable selection.

Associations between breathlessness severity, unpleasantness and the S−U difference, and QoL (higher scores indicating better perceived QoL) were analyzed using the multilevel linear mixed regression with random intercepts and slopes.

To explore the influence of ratings near the extremes of the scale, all analyses were repeated excluding assessments with severity <10 and >90 on the 100-mm VAS. Significance level was set as 0.05. All the analyses were conducted using Stata, version 14.2 (StataCorp LP, College Station, TX, 2016).

Table 1
Baseline Characteristics of 265 Patients With Severe Disease

Factor (Available Observations)	
N	265
Age, years ($N = 265$)	74.4 ± 9.2
Male ($N = 265$)	166 (62.6%)
BMI, kg/m^2 ($n = 254$)	25.7 ± 7.3
Main underlying diagnosis ($N = 265$)	
COPD	160 (60.4%)
Cancer	43 (16.2%)
Mixed	31 (11.7%)
Other	31 (11.7%)
Charlson Comorbidity Index score ($n = 264$)	3.2 ± 2.5
AKPS score ($n = 265$)	61.7 ± 10.0
mMRC breathlessness score ($n = 239$)	
1	30 (12.5%)[a]
2	46 (17.4%)
3	64 (24.2%)
4	99 (37.4%)
Missing	26 (9.8%)
Reported descriptors per participant ($n = 157$)	3 (3, 3)[b]
Number of sensory qualities per participant ($n = 157$)	2 (2, 2)[b]
Sensory qualities of breathlessness ($n = 157$)	
Air hunger	108 (40.8%)
Physical breathing effort	57 (21.5%)
Chest tightness	30 (11.3%)
Hyperpnea	65 (24.5%)
Mental breathing effort	39 (14.7%)
Missing	108 (40.8%)

AKPS = Australia-modified Karnofsky Performance Status; BMI = body mass index; mMRC = modified Medical Research Council.
Data presented as mean ± standard deviation or frequency (percentage) unless otherwise specified. The percentages for sensory qualities sum to more than 100 as participants could select up to three sensory descriptors.
[a]Participants were required to have an mMRC breathlessness score ≥ 2 at screening to be included, and these are the mMRC scores at study baseline.
[b]Median (interquartile range).

Results

Population

At 14 Australian centers between 2010 and 2014, 284 patients were randomized to morphine ($n = 145$) or placebo ($n = 139$). In total, 265 patients who had at least one paired measurement of severity and unpleasantness were included in the analysis (Table 1). Mean age of the participants was 74.4 years (SD 9.2); 166 (62.6%) were men; main underlying chronic diagnoses were COPD (60.4%) and cancer (16.2%); and 163 (61.6%) participants had an mMRC breathlessness score of 3 or 4 at baseline (Table 1). Data on sensory qualities of breathlessness were provided by 157 participants (59.2%), where participants selected a median of two descriptors that best matched their breathlessness sensation. The most common sensory qualities were air hunger, physical breathing effort, and hyperpnea (Table 1).

Distribution of Severity and Unpleasantness Scores

There were a total of 3630 paired measurements of severity and unpleasantness (Table 2), a median of 15 (IQR 14–16, of a maximal 16) per patient. Over the eight days, mean breathlessness severity was 37.1 mm and mean breathlessness unpleasantness was 35.0 mm on a 100-mm VAS. Severity and unpleasantness scores were highly correlated, $r = 0.856$ (Figure S2 in the online supplement). The variability was similar for severity and unpleasantness scores (SD 24.7 vs. 25.0). Both severity and unpleasantness varied more *between* participants than between measurements *within* each participant over time (Table 2).

Across all measurements, the mean S–U difference was 2.06 mm (SD 13.3; Table 2). The S–U differences were approximately normally distributed (Figure S1 in the online supplement), and the variability was similar across the eight days (Figure 1). In contrast to the separate severity and unpleasantness scores, the S–U difference varied less between participants ($SD_{between}$ 6.8) than between measurements in the same individual (SD_{within} 11.6; Table 2).

Agreement Between Severity and Unpleasantness

Agreement between severity and unpleasantness scores are shown in the Bland-Altman plot in Figure 2. The agreement was similar across the 16 measurement points (Figure S3 in the online supplement). As expected, the S–U differences were lower and less variable for scores near the extremes of the VAS (0 and 100). The S–U differences were symmetrically distributed above (I > U) and below (I < U) zero throughout the scale. The limits of agreement for severity and unpleasantness were −24.0 to +28.2 mm (Figure 2). The variability for the S–U difference was lower than that for severity and unpleasantness separately (Table 2); coefficient of repeatability was lower for the S–U difference (32.1 mm) than for

Table 2
Breathlessness Severity and Unpleasantness Measured Over Eight Days

Variable		Mean	SD Overall	SD Between Participants	SD Within Participants
Severity (100-mm VAS)	Overall	37.1	24.7	19.8	14.9
Unpleasantness (100-mm VAS)	Overall	35.0	25.0	20.1	15.1
S–U difference (mm)	Overall	2.06	13.3	6.8	11.6

S = severity of breathlessness; SD = standard deviation; U = unpleasantness of breathlessness; VAS = visual analogue scale.
Self-rated breathlessness severity, unpleasantness, and the difference between severity and unpleasantness (S–U difference) in the morning and evening during eight days. In total, 3630 assessments in 265 participants with a median of 15 (interquartile range 14–16 of a maximal 16) assessments per participant.

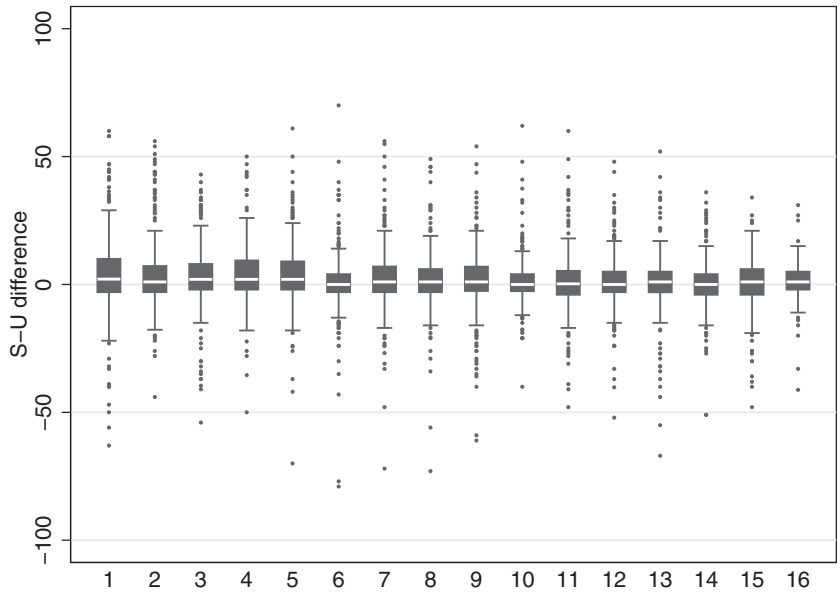

Fig. 1. Difference between paired severity (S) and unpleasantness scores for chronic breathlessness across morning and evening assessments during 8 days. Severity and unpleasantness were measured using 100-mm visual analogue scales (3630 paired scores in 265 people).

severity (41.3 mm) and unpleasantness (41.8 mm). Thus, agreement between severity and unpleasantness was better than expected from the variability in the individual scores.

Associations with the S−U Difference

Associations between the magnitude of S−U difference and clinical factors are shown in Table 3. People rating better QoL had a larger mean S−U difference, reflecting that they had relatively lower unpleasantness scores. The S−U difference was similar for ratings in the morning and evening but decreased slightly with time although the change was small (Figure 2). In multivariable analysis, the S−U difference was not independently associated with any of the evaluated clinical factors and did not vary by age, sex, morphine

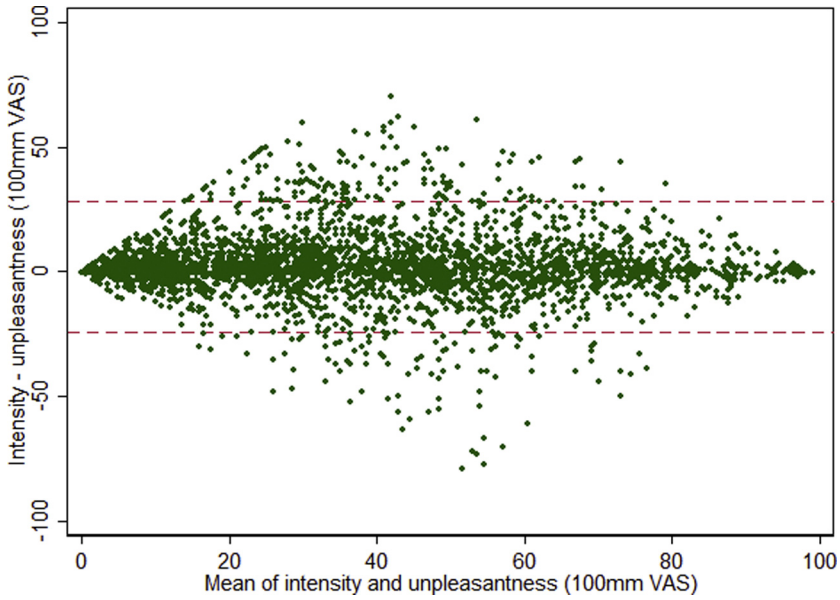

Fig. 2. Bland-Altman plot of agreement between paired severity (S) and unpleasantness scores of breathlessness. The mean difference between breathlessness severity and unpleasantness was 2.06 mm on a 100-mm visual analogue scale (VAS). The limits of agreement were −24.0 to +28.2 mm (lines).

Table 3
Associations With the Magnitude of Difference Between Severity and Unpleasantness in Chronic Breathlessness

	Univariable Analysis			Multivariable Analysis		
Factor	Change in S−U Difference (mm)	95% CI	*P*-value	Change in S−U Difference (mm)	95% CI	*P*-value
Age (per 1y)	0.002	−0.08 to 0.09	0.96	−0.04	−0.19 to 0.12	0.64
Male sex	0.86	−0.79 to 2.52	0.31	0.78	−2.23 to 3.79	0.61
Time (per 12 hours)	−0.32	−0.45 to −0.19	<0.001	−0.44	−0.65 to −0.22	<0.001
Evening vs. morning scores	0.05	−0.70 to 0.80	0.89	−0.18	−1.23 to 0.87	0.74
Morphine vs. placebo	−0.03	−0.11 to 0.05	0.50	1.15	−1.58 to 3.88	0.41
BMI (per 1 kg/m2)	0.64	−0.98 to 2.26	0.44	−0.11	−0.29 to 0.08	0.26
AKPS (per 1 point)	−0.12	−0.23 to −0.02	0.019	−0.06	−0.22 to 0.09	0.43
QoL (per 1 point; higher scores reflect better QoL)	0.73	0.29 to 1.18	0.001	0.62	−0.06 to 1.30	0.074
COPD vs. other	−0.27	−0.59 to 0.06	0.107	−2.37	−5.72 to 0.97	0.164
Charlson score (per 1 point)	−0.07	−1.66 to 1.52	0.93	−0.51	−1.23 to 0.22	0.169
mMRC at baseline			0.28[a]			0.12[a]
1	−0.13	−2.94 to 2.68	0.93	0.66	−3.95 to 5.27	0.78
2	2.09	−0.27 to 4.46	0.08	4.18	0.57 to 7.78	0.023
3	1.26	−0.88 to 3.40	0.25	2.83	−0.76 to 6.43	0.123
4	1.00			1.00		
No. reported descriptors	−0.53	−2.09 to 1.04	0.51	—	—	—
No. sensory qualities	−0.57	−2.07 to 0.94	0.46	—	—	—
Sensory qualities of breathlessness						
Air hunger	−0.24	−2.52 to 2.03	0.83	−0.75	−4.13 to 2.63	0.67
Physical breathing effort	−0.96	−3.17 to 1.25	0.40	−2.55	−5.79 to 0.69	0.123
Chest tightness	0.76	−1.92 to 3.44	0.58	2.44	−1.19 to 6.08	0.187
Hyperpnea	−0.30	−2.45 to 1.86	0.79	−1.75	−5.04 to 1.54	0.29
Mental breathing effort	−1.32	−3.72 to 1.09	0.28	−1.10	−4.44 to 2.25	0.52

CI = confidence interval; S = severity of breathlessness; U = unpleasantness of breathlessness; AKPS = Australia-modified Karnofsky Performance Status; BMI = body mass index; mMRC = modified Medical Research Council; QoL = quality of life.
Associations between clinical factors and the difference between paired self-rated breathlessness severity and unpleasantness (S−U difference) in 265 people (3630 measurements) with severe disease. Analyses were conducted using multilevel linear regression with random intercepts and slopes, accounting for repeated measurements. Estimates were calculated, unadjusted for each factor separately and adjusted for all factors in the model (multivariable analysis).
[a]*P*-value for the variable including all subcategories using likelihood ratio test.

treatment, BMI, functional status (AKPS), underlying main diagnosis, CCI score, mMRC, or with the presence of different sensory qualities of breathlessness (Table 3).

Associations with Perceived QoL

Associations with worse perceived QoL (lower QoL scores) were similar for higher breathlessness severity (−0.015; 95% CI, −0.018 to −0.011; $R^2 = 0.14$; $P < 0.001$) and unpleasantness (−0.019; 95% CI, −0.022 to −0.015; $R^2 = 0.17$; $P < 0.001$).

Sensitivity Analysis

All findings were similar when excluding assessments with severity <10 or >90 on the 100-mm VAS. The mean S−U difference was 2.7 mm (SD 14.3) overall, with SD 7.7 between participants and SD 12.3 within participants. Associations with clinical factors and QoL were similar as in the main analysis.

Discussion

Main Findings

The key findings, in people living with chronic breathlessness, were that 1) over eight days, ratings of breathlessness severity and unpleasantness were highly correlated, had similar variability, and varied more between patients than within patients; 2) the mean S−U difference was small (2.1 mm on a 100-mm VAS compared with the minimal clinically important difference in chronic breathlessness severity of 5.5 mm),[40] and agreement between severity and unpleasantness was higher than expected from the variability in individual scores; 3) the S−U difference was similar across a range of evaluated clinical factors including age, sex, diagnosis, morning and evening assessments, mMRC, morphine treatment, and presence of different sensory qualities of breathlessness; and 4) higher severity and unpleasantness were associated with worse perceived overall QoL in a similar manner.

What This Paper Adds

This is the first longitudinal study focused on the agreement between the overall breathlessness severity and unpleasantness in a clinical population with chronic breathlessness. The study reports novel data on variability of these breathlessness dimensions between patients and over time, the influence of clinical factors on the scores, and the associations of the severity and unpleasantness with worsening perceived QoL. Our data show that the difference between them

measured across eight days is small and both measures relate to other clinical factors in a similar manner.

Overall severity of breathlessness was assessed using the question ("How is your breathlessness right now?") with a maximum anchored at "worst possible," which is consistent with previous studies [24,25,28,29] and the revised Edmonton Symptom Assessment System (ESAS-r) instrument.[41] Under controlled conditions including known and scalable stimuli, there are evidence that people with and without chronic breathlessness can differentiate between intensity and unpleasantness of breathlessness.[17–19] In daily life settings, the relationship between overall severity and overall intensity of breathlessness has not been clearly delineated in the literature and cannot be inferred from the present findings. Furthermore, the terms and wordings have often been used interchangeably in studies, without cognitive validation with patients to examine how well the questions elicit distinct constructs. The present agreement between overall severity and unpleasantness scores is in line with observations during development of the MDP that the overall intensity and unpleasantness scores tracked together and that the overall unpleasantness score (A1) clustered with the intensities of the different sensory qualities.[15,42–44] The present findings support the decision to include only one of the overall scores (unpleasantness) in the MDP.[15]

Importantly, the present findings do not mean that severity and unpleasantness reflect the same underlying construct and do not contradict previous reports that breathlessness intensity can to some extent be differentiated from unpleasantness by the individual in the laboratory setting.[1,13,17,18,45] The present study provides novel data on the agreement between repeated severity and unpleasant ratings in daily life of patients with chronic breathlessness. On the group level, mean breathlessness severity and unpleasantness scores were comparable, with a small mean difference and variability that is similar or lower than that expected from the variability in the individual severity and unpleasantness scores. The comparison of the variability is important as the maximal agreement that is possible to obtain is limited by the level of random variability in the severity and unpleasantness. Even if the actual agreement was perfect, the observed agreement would be decreased in relation to random variation in the scores that are compared.[38] In the present analysis, the systematic (mean) difference was small and there was no evidence for additional lack of agreement between severity and unpleasantness above that expected from the variability in each score. The comparability of the scores is further supported by the similarity of associations between severity and unpleasantness across the evaluated clinical factors and their similar associations with perceived QoL. The S−U difference decreased slightly over the eight days, which might reflect increasing familiarity of participants with the rating system over time.

Strengths and Limitations

Data were collected longitudinally using validated instruments focused on the participants' current experience of breathlessness and a number of relevant clinical factors. Symptoms and QoL were self-rated with no proxy reports. Data were of high quality and completeness for a phase III clinical trial conducted in accordance with the Good Clinical Practice guidelines. Multivariable models accounted for repeated measurements and evaluated the interplay of multiple clinical important factors.

A limitation is that data on sensory qualities were available for a subset of patients, but the associations were adjusted for differences in other available clinical factors. Data were unavailable on the intensity for separate sensory qualities of breathlessness, which should be explored using multidimensional instruments in further research.[15] Ratings were of current breathlessness in the morning and evening of each day in daily life, which was similar for the severity and unpleasantness scores. However, the question relating to severity ("how is your breathlessness") might have been interpreted by the patient as enquiring about the quality rather than quantity of their breathlessness, and the upper anchor ("worst possible") might have implied distress or unpleasantness in some participants. Many breathlessness trials including studies of acute breathlessness have not measured distress or unpleasantness as distinct from severity, and the construct measured thus may have been a mixture of the two. The present findings pertain to chronic breathlessness and cannot necessarily be extrapolated to acute or acute-on-chronic or instances of episodic breathlessness where accompanying distress and panic may change the interplay between perceived severity and unpleasantness. For example, the minimal clinical important difference in breathlessness in acute asthma and acute pulmonary edema is approximately twice that as for chronic breathlessness.[46,47] In the safe environment of an emergency department, a patient's level of distress may subside before the severity, and thus the perception of unpleasantness may be differentially affected.

Implications

The present findings show a high degree of agreement between overall severity and unpleasantness of breathlessness at a group level indicating that participants did not reliably or consistently discriminate between the two symptom questions. These findings

support the notion that assessment of one, rather than both breathlessness domains, may be sufficient for many research and clinical settings where participants are anticipated to be in a stable condition. In day-to-day clinical care, unidimensional scales (VAS or NRS) for breathlessness severity and unpleasantness allow time-efficient assessment. Routine measurement in clinical practice has been successfully implemented for breathlessness severity.[26,48] Similar to pain, the unpleasantness relating to breathlessness is distressing, results in immediate and longer-term behavioral responses, and should be addressed in clinical care using evidence-based nonpharmacological and pharmacological interventions.

The choice of instrument and dimension(s) of measurement ultimately depends on the setting, population (acceptable burden to patients), available time and resources, as well as the aim of measurement. Importantly, the effect of interventions might differ between breathlessness dimensions. For instance, pulmonary rehabilitation has been shown to mainly decrease the affective and functional impact of breathlessness,[49] and opioids might have a stronger effect on the affective dimension and especially decrease unpleasantness or anxiety-related to breathlessness.[50,51] There may therefore be settings and contexts (acute, acute-on-chronic, and episodic breathlessness) where both breathlessness severity and unpleasantness should be measured or where one of the dimensions should be preferentially assessed instead of another. Further research should clarify the most appropriate question wording to elucidate quantity of breathlessness and validate the current findings in other clinical populations and settings and determine the minimal clinically important difference in breathlessness unpleasantness.

Disclosures and Acknowledgments

Conflicts of interest: D. C. C. has received an unrestricted research grant from Mundipharma, is an unpaid member of an advisory board for Helsinn Pharmaceuticals and Specialist Therapeutics, and has consulted to Mayne Pharma and received intellectual property payments from them. M. J. J. has consulted to Mayne Pharma. M. E. and M. W. have no conflicts of interest to disclose.

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Online Supplement

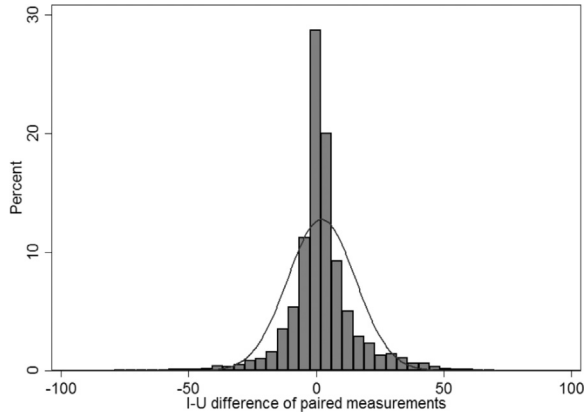


Fig. S1. Differences between paired overall severity (I) and unpleasantness scores of chronic breathlessness. The bell curve represents a normal distribution.

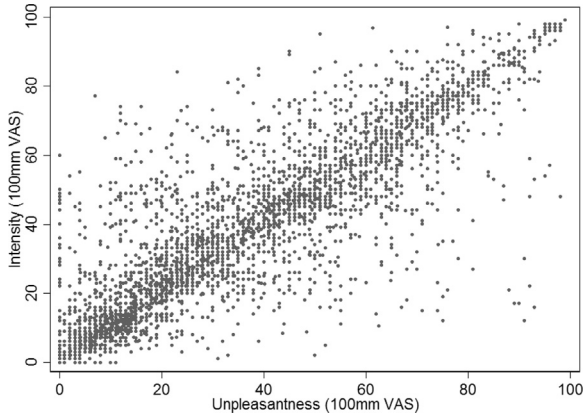


Fig. S2. Relation between paired measurements of breathlessness severity and unpleasantness.

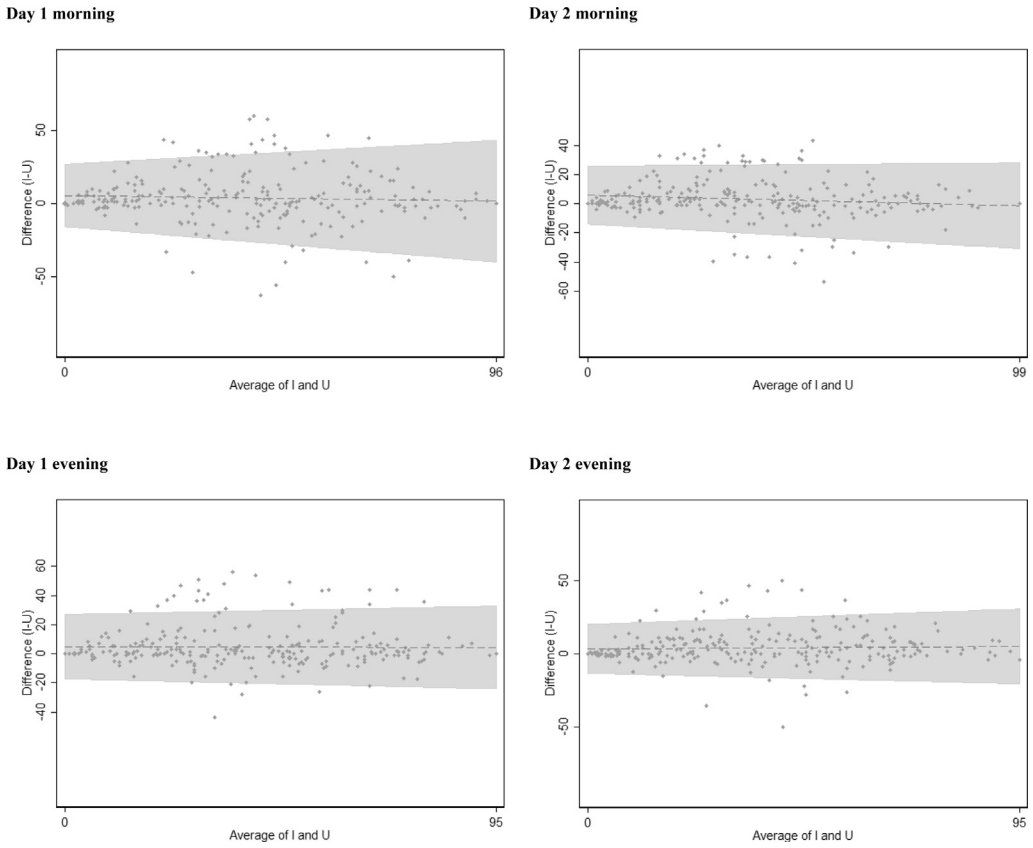


Fig. S3. Agreement between paired breathlessness severity (I) and unpleasantness (U) scores at each of the 16 assessments (morning and evening) over 8 days. Mean difference (dashed line) with 95% limits of agreement (shaded area).

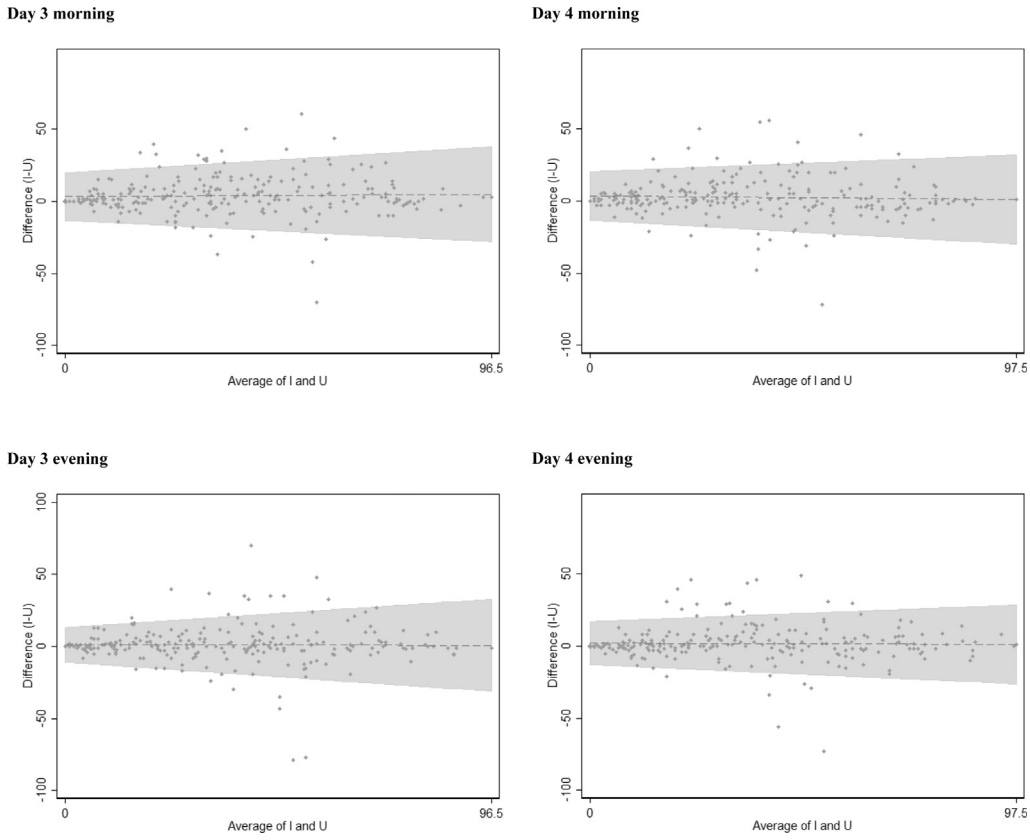
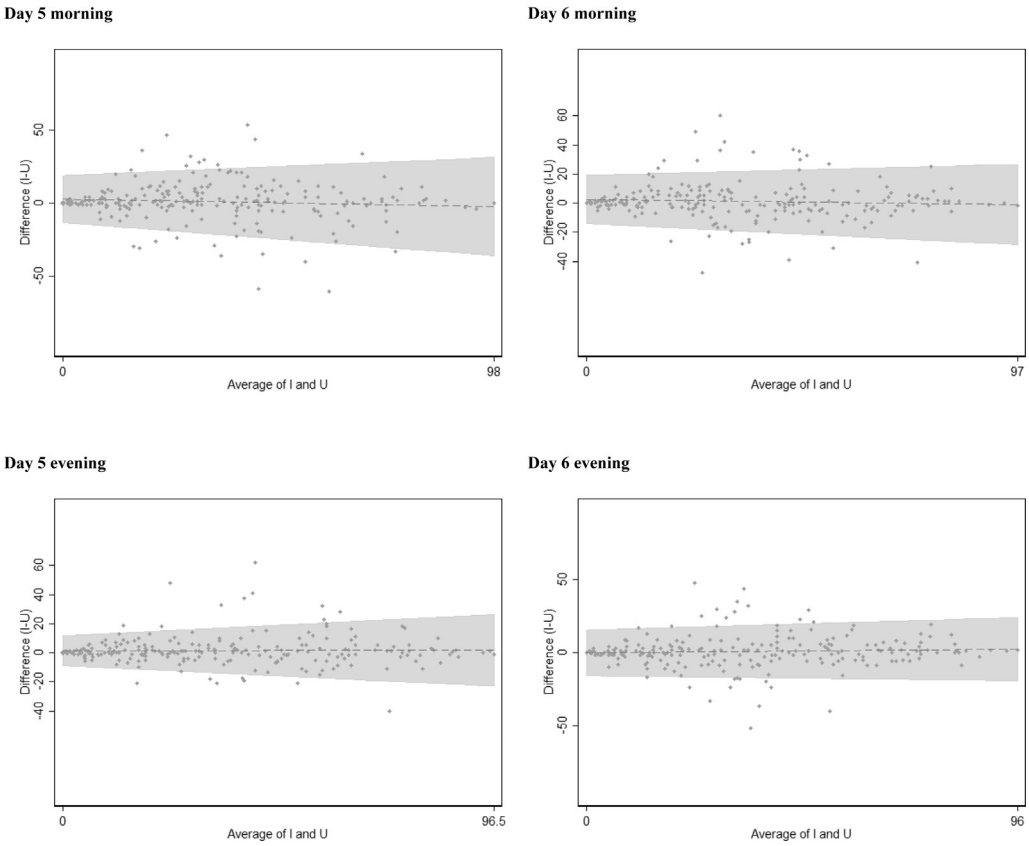


Fig. S3. *(Continued)*



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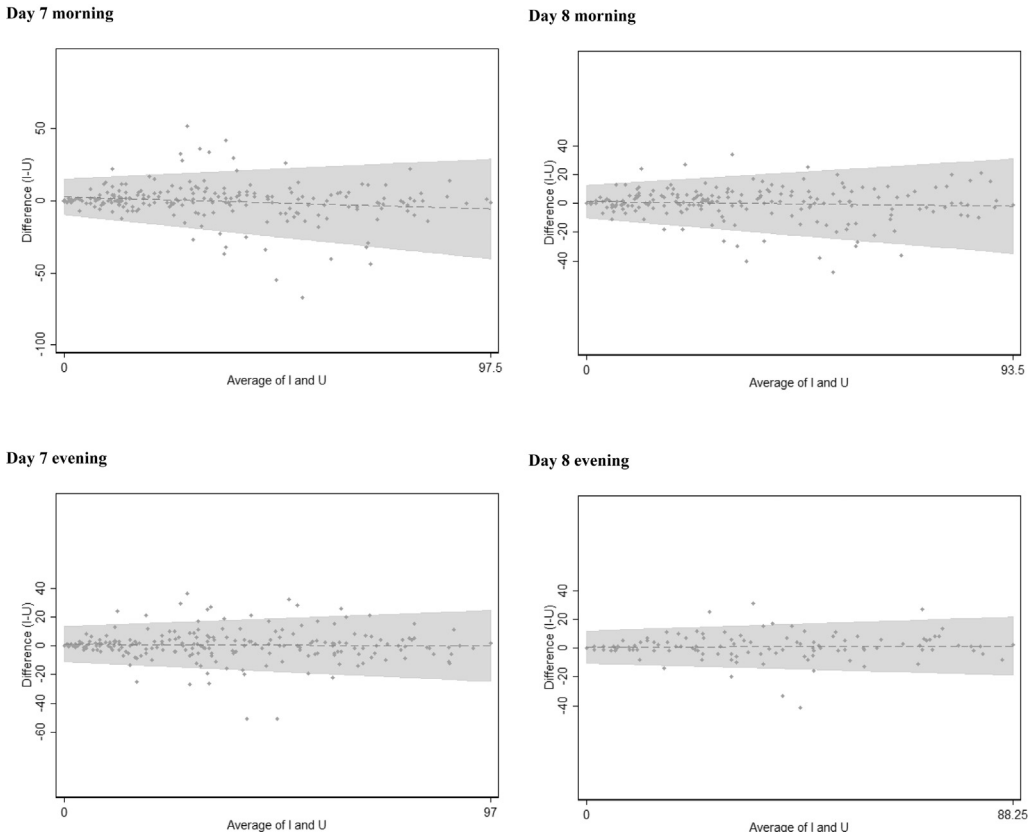

Fig. S3. *(Continued)*