

Impact of a Specialized Ambulatory Clinic on Refractory Breathlessness in Subjects With Advanced COPD: A Retrospective Analysis

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BACKGROUND: Severe exertional dyspnea is a commonly reported symptom in patients with COPD, especially in the advanced stages. Our objective was to assess the preliminary impact of comprehensive, individualized management provided by a specialized tertiary center clinic on exertional dyspnea and patient-centered outcomes in patients with advanced COPD. **METHODS:** This retrospective analysis included 45 subjects with COPD who were evaluated in a newly established dyspnea clinic over 3 years. Those with severe exertional dyspnea (Medical Research Council dyspnea score of $\geq 4/5$), despite optimal disease-targeted therapy were eligible for referral. We used the revised Edmonton Symptom Assessment System (ESAS-r) to assess symptoms. Responders were defined as those whose change from baseline to 2-months met the minimum clinically important difference of ≤ -1 in ESAS-r score for shortness of breath. **RESULTS:** Subjects (mean \pm SD age 70 ± 7 years) had an average FEV₁ of $36 \pm 18\%$ predicted and a Medical Research Council dyspnea score of 4.7 ± 0.4 . Responses to the intervention were variable and mean change in the ESAS-r score for shortness of breath in the total group was -0.32 ± 3.39 , $P = .53$. Forty-seven percent of the subjects were identified as responders, and 42, 40, 40, and 33% met the minimum clinically important difference for improvement in ESAS-r scores for tiredness, anxiety, well-being, and depression, respectively. Responders had fewer emergency department annual visits in the 2 years after their first clinic visit compared with nonresponders (mean \pm SD, 1.38 ± 1.63 vs 4.45 ± 5.52 , $P = .034$). **CONCLUSIONS:** Although the impact of our specialized advanced dyspnea clinic was variable, as evaluated by the ESAS-r, it provided measurable additional clinically important benefit to almost half of the subjects with advanced COPD and severe refractory dyspnea. *Key words:* dyspnea; COPD; comprehensive management; palliative care. [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Breathlessness (dyspnea) is the most commonly reported symptom in patients with COPD, a devastating disease predicted to be the third leading cause of death worldwide

by 2020.^{1,2} The severity of dyspnea increases with age and disease progression,³ and is a more accurate predictor of mortality among patients with COPD than is impairment

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INTEGRATIVE MANAGEMENT OF SEVERE BREATHLESSNESS IN COPD

of lung function.⁴ In fact, as many as 95% of patients with advanced COPD experience breathlessness during minimum exertion.⁵ In addition, such patients exhibit many other comorbid conditions that contribute to respiratory discomfort and decreased cardiorespiratory fitness related to a sedentary lifestyle.²

Evidence-based pharmacologic and nonpharmacologic treatment options for breathlessness in patients with chronic respiratory diseases are sparse and are generally underused.⁶⁻⁸ Apart from the use of bronchodilators and inhaled corticosteroids, as the first step in dyspnea management in patients with COPD, a variety of drugs have been proposed for treatment of breathlessness (eg, opioids, benzodiazepines, methotrimeprazine, cannabinoids),^{6,9} but there is little concrete evidence to support their routine use. In this context, a trial of opiates has been recommended as a treatment for refractory dyspnea in selected patients with COPD.⁶

Despite our increased understanding of the complex neurobiology of dyspnea, effective dyspnea relief for many individuals remains an elusive goal. To address the growing need to improve quality of life in patients with advanced COPD who remain breathless despite optimal disease-targeted pharmacotherapy, we established a new advanced dyspnea clinic at our center under the leadership of a palliative care specialist, nurse practitioner, and respirologists, with a particular interest in refractory dyspnea management. Only patients with chronic severe exertional dyspnea, defined by a score of ≥ 4 of 5 on the Medical Research Council (MRC) dyspnea scale,¹⁰ referred exclusively by a respiratory specialist, were eligible for assessment and treatment in this clinic. To our knowledge, this was the first clinic of its kind in Canada; the purpose of the current article was to describe the components of the program, to share our experience to date, and to examine its impact on patient-centered outcomes throughout the duration of treatment.

The overall rationale for effective management of dyspnea was, first, to optimize respiratory mechanics (bronchodilator combinations) as much as possible; second, in carefully selected patients, to reduce the increased respiratory neural drive to breathe (eg, supplemental oxygen, opiates), without clinically compromising alveolar ventilation; and third, to assist in improving quality of life as much as possible. These combined therapies would ensure that neuromechanical coordination of the respiratory system was partially restored to achieve an associated subjective benefit.^{6,9} Also, every attempt was made to address the often dominant affective and psychosocial components of severe dyspnea, and to offer individualized end-of-life counseling. We postulated that an integrated approach based on this rationale (see above) would provide important palliative care support for such patients and result in significant improvements in validated outcomes, such as symp-

QUICK LOOK**Current knowledge**

Severe exertional dyspnea is a commonly reported symptom in patients with COPD, especially in advanced stages. Evidence-based pharmacologic and nonpharmacologic interventions for dyspnea relief are available but generally underused. The role of comprehensive management and palliative care is well documented in symptomatic patients with thoracic cancer, but data about the role of similar service in improving symptoms and patient-centered outcomes in those with non-cancerous chronic respiratory diseases are sparse.

What this paper contributes to our knowledge?

The study provided new insights into the role of a specialized advanced dyspnea clinic in improving dyspnea and other patient-centered outcomes in subjects with advanced COPD. The comprehensive service provided through this clinic ensured a well-structured discussion about end-of-life care and provided measurable clinically important benefits to some subjects who were symptomatic. The positive preliminary results cannot be generalized but do set the stage for new randomized studies to evaluate the role of specialized clinics for palliative care in patients with chronic respiratory diseases and refractory dyspnea despite disease-specific therapy.

tom severity scores when using the revised version of the Edmonton Symptom Assessment System (ESAS-r).¹¹ We, therefore, undertook a retrospective pre-post analysis to examine the impact of comprehensive integrated management provided by this specialized clinic on symptoms (ESAS-r as a primary outcome) and other important patient-centered outcomes (hospital admission and emergency visits as a secondary outcome).

Methods**Subjects and Study Design**

This was a retrospective study that included patients with advanced COPD who had attended the advanced dyspnea clinic at Hotel Dieu Hospital and Kingston Health Sciences Centre (Kingston, Ontario, Canada) between 2013 and 2016 ($N = 62$). Given that the patients were not followed up at fixed and/or similar intervals, we identified 45 subjects of the 62 patients who had a follow-up visit between 1 and 3 months after the initial (baseline) visit and labeled this the 2-month follow-up visit to assess for symptomatic responses.

INTEGRATIVE MANAGEMENT OF SEVERE BREATHLESSNESS IN COPD

Table 1. Overall Pharmacologic and Nonpharmacologic Interventions Provided Through the Clinic

Pharmacologic	Nonpharmacologic
Optimization of disease-specific therapy	Referral for pulmonary rehabilitation
Short- and long-acting opiates with close monitoring of CO ₂ levels	Referral for community palliative care service
Methotrimeprazine	Sleep hygiene
Management of exacerbations	End-of-life discussion
Identifying and treating comorbidities	Psychosocial support and panic control
Oxygen therapy	Noninvasive ventilation
	Walkers and home equipment to assist with mobility and safety

The Queen's University and Affiliated Teaching Hospitals Research Ethics Board approved the analysis of these anonymous data sets (DMED-2187-18). Inclusion criteria were patients with a primary diagnosis of severe to very severe COPD and severe breathlessness (ie, an MRC dyspnea score of ≥ 4 of 5), despite optimum disease-specific pharmacotherapy and with at least one follow-up visit at this specialized clinic. Patients referred by respirologists and who met the inclusion criteria were evaluated by an experienced nurse practitioner (EH) and a palliative care physician specialist (IAH). The main components of individualized management of subjects

who attended this specialized clinic are outlined in Table 1 and Figure 1.

Data Collection

Data were collected from subjects' electronic and paper charts. All data were entered into one database for a multifactorial evaluation of subjects' outcome and well-being. Data included subjects' baseline characteristics (demographics and lung function tests), symptom questionnaires at baseline and over the treatment period, and interventions (pharmacologic and nonpharmacologic) that were first introduced through this clinic. In addition, information about the frequency of (and reason for) annual hospital admissions and emergency department (ED) visits 1 year before and 2 years after the first clinic visit were collected.

Questionnaires included MRC dyspnea scale,¹⁰ ESAS-r (as a primary outcome),¹¹ and palliative performance scale.¹² The ESAS-r is a 9-item scale: the 9 items are pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, and well-being.¹¹ The ESAS-r numerically rates each of these items on a 0–10 scale, 0 being none (absence of symptoms) and 10 being the worst possible severity.^{11,13,14} The minimum clinically important difference cutoff for improvement/deterioration in ESAS-r was found to be 1/–1 for individual item scores.^{13,15} The palliative performance scale ranges, in 10% increments, from 0–100%, in which 0% indicates death and 100% indicates full performance.¹²

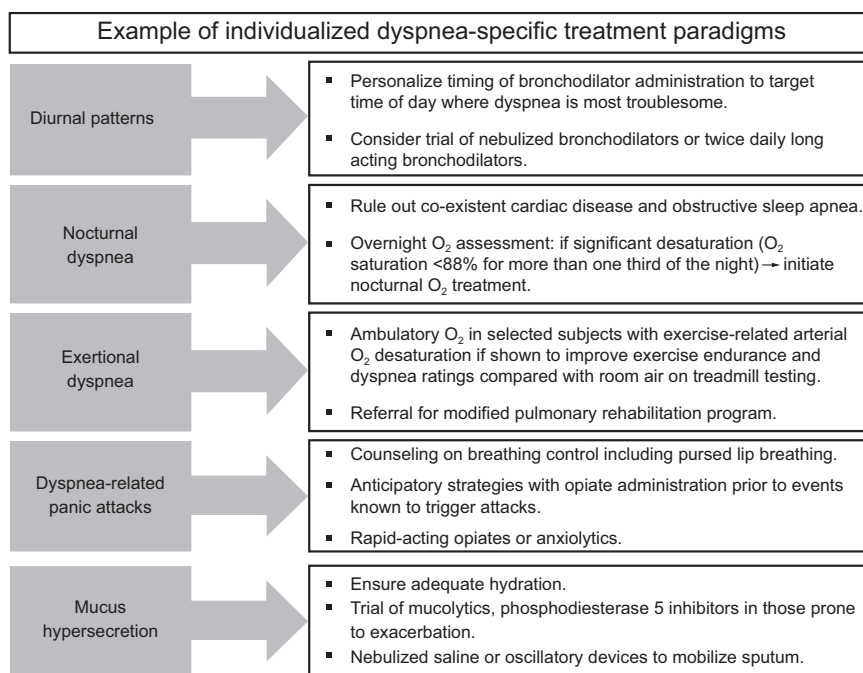


Fig. 1. Example of individualized dyspnea-specific treatment paradigms offered to the subjects during the clinic visit.

INTEGRATIVE MANAGEMENT OF SEVERE BREATHLESSNESS IN COPD

Statistical Analysis

Data were analyzed by using the Statistical Package for Social Sciences (SPSS ver. 24) and SAS software (SAS ver.9.4TS1M4, SAS/STAT ver.14.3) (SAS Institute, Cary, North Carolina). A change in ESAS-r symptoms score for the shortness of breath domain over the treatment period was the primary outcome measure. Secondary outcome measures included frequency of ED visits and hospital admissions 2 years after the first clinic visit. We also quantified the numbers of program participants availing, for the first time, of structured end-of-life discussions.

The paired *t* test was used to examine the changes in ESAS-r scores, and the Wilcoxon signed-rank test was used to compare ED visits and hospital admission in the year before and the second year after the first clinic visit. Responders were defined as those who met the minimum clinically important difference (≤ -1) for the ESAS-r score for shortness of breath domain at follow-up. The Fisher exact test was used to compare binary variables, the 2-sample *t* test was used to compare age, baseline lung function tests and the Wilcoxon rank-sum test was used to compare body mass index, annual ED visits, and hospital admission between responders and nonresponders. We considered $P < .05$ statistically significant, and due to the exploratory nature of this analysis, we did not correct for multiplicity of tests.

Results

Subject Characteristics and Interventions Through the Clinic

Sixty-two patients with advanced COPD attended this clinic between 2013 and 2016. As stated in the methods section, the current analysis included only 45 subjects of 62 patients who had a follow-up visit between 1 and 3 months after the initial (baseline) visit. The patients excluded from the pre-post analysis did not have a follow-up visit within the pre-specified time frame, or were lost to follow up, or enrolled in a community palliative outreach clinic. At their first visit, the subjects had severe to very severe airway obstruction (FEV_1 of $36 \pm 18\%$ predicted, mean \pm SD) and the majority (84%) were ex-smokers. The subjects had evidence of resting hyperinflation (total lung capacity of 135 ± 34 and functional residual capacity of 179 ± 49 , both as percent predicted), pulmonary gas trapping (residual volume per total lung capacity: $62 \pm 12\%$), and moderate reduction in lung diffusing capacity for carbon monoxide ($50 \pm 14\%$ predicted). As per referral requirements, the subjects had severe chronic activity-related dyspnea (MRC dyspnea score of 4.7 ± 0.4 [mean \pm SD]). Twenty-seven subjects (60%) were already on oxygen therapy before referral. The general baseline

Table 2. Subjects' Baseline Characteristics

Characteristic	Results
Men/women, <i>n</i>	25/20
Age, mean \pm SD y	70 \pm 7
Body mass, mean \pm SD kg	68 \pm 21
Height, mean \pm SD cm	162 \pm 18
BMI, mean \pm SD kg/m ²	29 \pm 17
Smoking status, <i>n</i> (%)	
Current	4 (9)
Ex-smoker	38 (84)
Not available	3 (7)
Smoking history, mean \pm SD pack-year	47 \pm 19
MRC dyspnea score (1–5), mean \pm SD	4.7 \pm 0.4
Baseline PPS, mean \pm SD %	58 \pm 7
Pulmonary function test, mean \pm SD	
FEV ₁ , % predicted	36 \pm 18
FVC, % predicted	66 \pm 17
FEV ₁ /FVC, %	37 \pm 12
Inspiratory capacity, % predicted	74 \pm 24
TLC, % predicted	135 \pm 34
FRC, % predicted	179 \pm 49
RV, % predicted	224 \pm 77
RV/TLC, %	62 \pm 12
D _{LCO} , % predicted	50 \pm 14
D _{LCO} /V _A , % predicted	65 \pm 20
TLC-V _A , L	3.68 \pm 1.34
Inhaled medications, <i>n</i> (%)	
SABA	40 (89)
SAMA	17 (38)
LABA	1 (44)
LAMA	36 (80)
ICS	4 (41)
ICS/LABA	40 (89)

N = 45.

BMI = body mass index

MRC = Medical Research Council

PPS = palliative performance scale

TLC = total lung capacity

FRC = functional residual capacity

RV = residual volume

D_{LCO} = diffusing capacity of the lung for carbon monoxide

V_A = alveolar volume measured by single breath gas dilution

D_{LCO}/V_A = D_{LCO} corrected for alveolar volume

SABA = short-acting β_2 -agonist

SAMA = short-acting muscarinic antagonist

LABA = long-acting β_2 -agonist

LAMA = long-acting muscarinic antagonist

ICS = inhaled corticosteroid

characteristics of the subjects and inhaled medications are summarized in Table 2. Almost all the subjects were on triple inhaled therapy. Fourteen of the 45 subjects (31%) were deceased at the time of the analysis.

Comorbid conditions were anxiety and/or depression (53% of the subjects), systemic hypertension (38%), and obstructive sleep apnea (31% [all were on CPAP]), extrapulmonary cancer (20%), pulmonary hypertension (18%), well-controlled heart failure (16%), ischemic heart

INTEGRATIVE MANAGEMENT OF SEVERE BREATHLESSNESS IN COPD

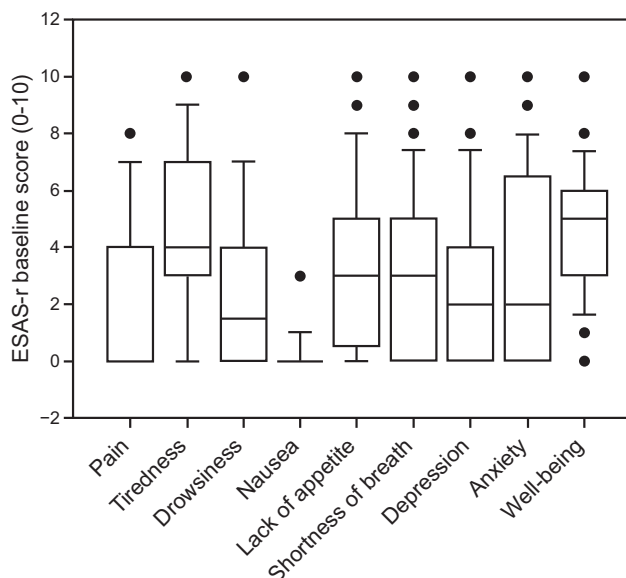


Fig. 2. Baseline revised Edmonton Symptom Assessment System (ESAS-r) score of the 9 domains in subjects with COPD. Boxes depict the first to third quartile (ie, the middle half of the data), whereas the center line shows the median. Whiskers range from the 10th to the 90th percentile.

Table 3. Interventions Through the Specialized Dyspnea Clinic

Intervention	Subjects, <i>n</i> (%)
Smoking cessation advice and/or support to current smokers (<i>n</i> = 4)	4 (100)
Review of inhaled therapy technique	45 (100)
Sleep hygiene	14 (31)
Self-management plan	45 (100)
Pharmacologic	
Opioids	40 (89)
Methotrimeprazine	14 (31)
Nutritional advice	11 (24)
Referral to community palliative care	24 (53)
New oxygen therapy prescription	14 (31)
End-of-life discussion	37 (82)

disease (13%), and well-controlled diabetes mellitus (11%). At the time of the study, 22 subjects (49%) had previously participated in a pulmonary rehabilitation program, and none participated in this program after the first clinic visit. Baseline ESAS-r scores for all domains are shown in Figure 2, and the baseline ESAS-r score for the shortness of breath domain was 3.07 ± 2.86 (mean \pm SD).

Interventions first introduced through the clinic are summarized in Table 3. Eighty-nine percent of the subjects were prescribed systemic opioids to control their refractory breathlessness, and 31% were prescribed methotrimeprazine. Opioids were prescribed in the form of hydromorphone controlled-release (3, 6, or 12 mg every 12 h and/or

hydromorphone 0.5–2 mg every 4 h as a breakthrough intervention, and a few subjects (*n* = 6) were prescribed morphine instead, depending on the subject's status, comorbid condition, and response to initial dosage. The usual plan was to start with very-low-dose immediate-release hydromorphone (0.5 mg) given every 4 h (or morphine 2.5 mg every 4 h) and slowly titrating the dose to effect while balancing and managing potential opioid-related adverse effects. Once an effective dose was found, the subjects were switched to sustained-release hydromorphone (or morphine) formulations. The hydromorphone controlled-release dose did not exceed 15 mg every 12 h, and the morphine-controlled release dose did not exceed 40 mg every 12 h in any subject.

Immediate-release hydromorphone was provided in the subjects who were deemed reliable and to have a clear understanding of how to use a breakthrough dose. The subjects were educated to use a breakthrough dose ~30–40 min before activities that regularly caused increased breathlessness (eg, showering, going out of the house, before exercise). The subjects were specifically instructed not to use breakthrough doses for increased dyspnea related to an acute COPD exacerbation. If a subject had a tendency to overuse inhalers or other medications or if the subject had a history of substance abuse, then he or she was not prescribed a breakthrough opioid dose.

Fourteen subjects (31%) were prescribed long-term oxygen therapy for the first time through the clinic. Most subjects (82%) were involved in discussions related to their goals of care and the illness trajectory for COPD, and 53% of the subjects were referred to home and community care programs for palliative care supports in the home.

Primary and Secondary Outcomes

The median time for follow up was 1.61 months (interquartile range, 1.38–2.07 months). The primary and secondary outcomes in the whole sample (*N* = 45) are shown in Table 4. Responses to the intervention were variable and the mean change in ESAS-r score for shortness of breath in the total group was -0.32 ± 3.39 (*P* = .53). There were no differences in all other ESAS-r domains at follow-up except for a higher score for drowsiness. In the whole group, there were no differences in hospital admissions or ED visits at follow-up, whether this was for any reason or for a respiratory condition (all *P* > .05) (Table 4).

Responders Versus Nonresponder Subanalysis

Of the 45 subjects, 47% (*n* = 21) were identified as responders. The differences in ESAS-r scores for all domains at follow-up from baseline are shown in Figure 3.

INTEGRATIVE MANAGEMENT OF SEVERE BREATHLESSNESS IN COPD

Table 4. Primary and Secondary Outcomes in the Whole Sample

Variable	Baseline	Follow-up*
Primary outcome: ESAS-r scores (0–10), mean \pm SD		
Pain	1.98 \pm 2.65	2.18 \pm 3.01
Tiredness	4.71 \pm 3.10	4.69 \pm 2.76
Drowsiness	2.48 \pm 2.87	3.44 \pm 2.89†
Nausea	0.20 \pm 0.66	0.56 \pm 1.34
Lack of appetite	3.47 \pm 2.89	3.36 \pm 2.54
Shortness of breath	3.07 \pm 2.86	2.74 \pm 2.76
Depression	2.47 \pm 2.81	2.31 \pm 3.02
Anxiety	3.42 \pm 3.25	3.09 \pm 2.85
Well-being	4.44 \pm 2.31	4.69 \pm 2.56
Secondary outcome: annual hospital admission and ED visits, median (range)		
Admission due to any reason	1 (0–8)	0 (0–14)
Admission due to respiratory condition	0 (0–5)	0 (0–13)
ED visits due to any reason	1 (0–10)	1 (0–22)
ED visit due to respiratory condition	0 (0–7)	0 (0–12)

N = 45.
 * Follow-up for ESAS-r was the follow-up visit between 1 and 3 months after the initial (baseline) visit and was labelled as the 2-month visit for assessment of symptomatic responses. For the secondary outcome, the comparisons were made for annual visits in the year before and the second year after the first clinic visit.
 † *P* < .05 baseline vs follow-up.
 ESAS-r = revised version of the Edmonton Symptom Assessment System
 ED = emergency department

Apart from the shortness of breath domain, 42, 40, 40, and 33% of the 45 subjects met the minimum clinically important difference for improvement in ESAS-r score for domains of tiredness, anxiety, well-being, and depression, respectively. Comparisons between patients with COPD who were responders and nonresponders showed no significant differences in age, body mass index, baseline MRC dyspnea scale, or smoking history (Table 5). In addition, the 2 groups were similar in reported comorbidities and in the interventions applied through the clinic. The mean differences (between baseline and follow-up) for the ESAS-r score for domains other than shortness of breath were similar in the 2 groups except for well-being, which was better in responders (*P* = .044) (Table 5). The subjects who were responders had a higher baseline ESAS-r score for shortness of breath domain compared with nonresponders (4.86 \pm 2.63 vs 1.50 \pm 2.04, mean \pm SD, *P* < .001), but 50% of nonresponders had baseline ESAS-r scores for shortness of breath of \geq 1.

The subjects with COPD who were responders had fewer annual ED visits due to any reason in the second year after the first clinic visit compared with nonresponders (1.38 \pm 1.63 vs 4.45 \pm 5.52, *P* = .034). There was no difference between responders and nonresponders in the

frequency of annual hospital admissions (Fig. 4). The subjects who were nonresponders had more annual ED visits in the 2 years after the first visit compared with 1 year before their first clinic visit (4.45 \pm 5.52 vs 2.04 \pm 3.22; *P* = .01).

Discussion

The main findings of the current study were (1) our results did not meet the primary outcome of the study: mean ESAS-r scores were not different before and after enrollment in the advanced dyspnea clinic in the whole sample; and (2) A post hoc analysis identified responders (21/45) and nonresponders based on whether they reached the minimum clinically important difference for the dyspnea domain of the ESAS-r; responders had less frequent annual ED visits after being followed up in this specialized clinic compared with nonresponders.

The current study included a well-characterized group of subjects with advanced COPD (average FEV₁ of 36% predicted) who had severe exertional dyspnea as assessed by the MRC dyspnea scale. As previously reported,¹⁶ obstructive sleep apnea is a commonly reported comorbid condition in patients with COPD (31% of our sample), and all subjects with this diagnosis were using CPAP. In addition, 53% of the subjects with COPD had anxiety and/or depression defined at their initial assessment visit. Our results were in keeping with previous studies in which anxiety, panic disorders, or depression was reported in 20 to 60% of subjects with COPD, depending on the disease stage and the scale used.¹⁷⁻²⁰

The primary tenets of palliative care are to optimize symptom management and quality of life throughout the illness journey, plus establishment of goals of care that are in keeping with the patient's values and preferences. The role of palliative care comes into play when the usual disease-specific pharmacologic and nonpharmacologic treatment options are optimized. This specialized clinic was established with comprehensive care provided by a palliative care physician (IAH) and a nurse practitioner specialist (EH) to help patients with advanced COPD who have chronic severe exertional dyspnea (MRC dyspnea score of \geq 4 of 5), despite optimized disease-specific therapies. We used the MRC dyspnea scale to identify those with severe exertional dyspnea who may benefit from attending this clinic. The MRC scale is the most widely used dyspnea scale, which measures the magnitude of the task required to cause breathlessness and has been previously linked to health outcomes.²¹ By contrast, the ESAS-r, a patient-rated symptom severity numeric scale, was used to evaluate patients' symptoms, including shortness of breath at initial and follow-up visits.²²

At follow-up, subjects' responses, as assessed by using the ESAS-r, were variable and showed that, in the total sample, a change in the ESAS-r score for shortness of breath or an-

INTEGRATIVE MANAGEMENT OF SEVERE BREATHLESSNESS IN COPD

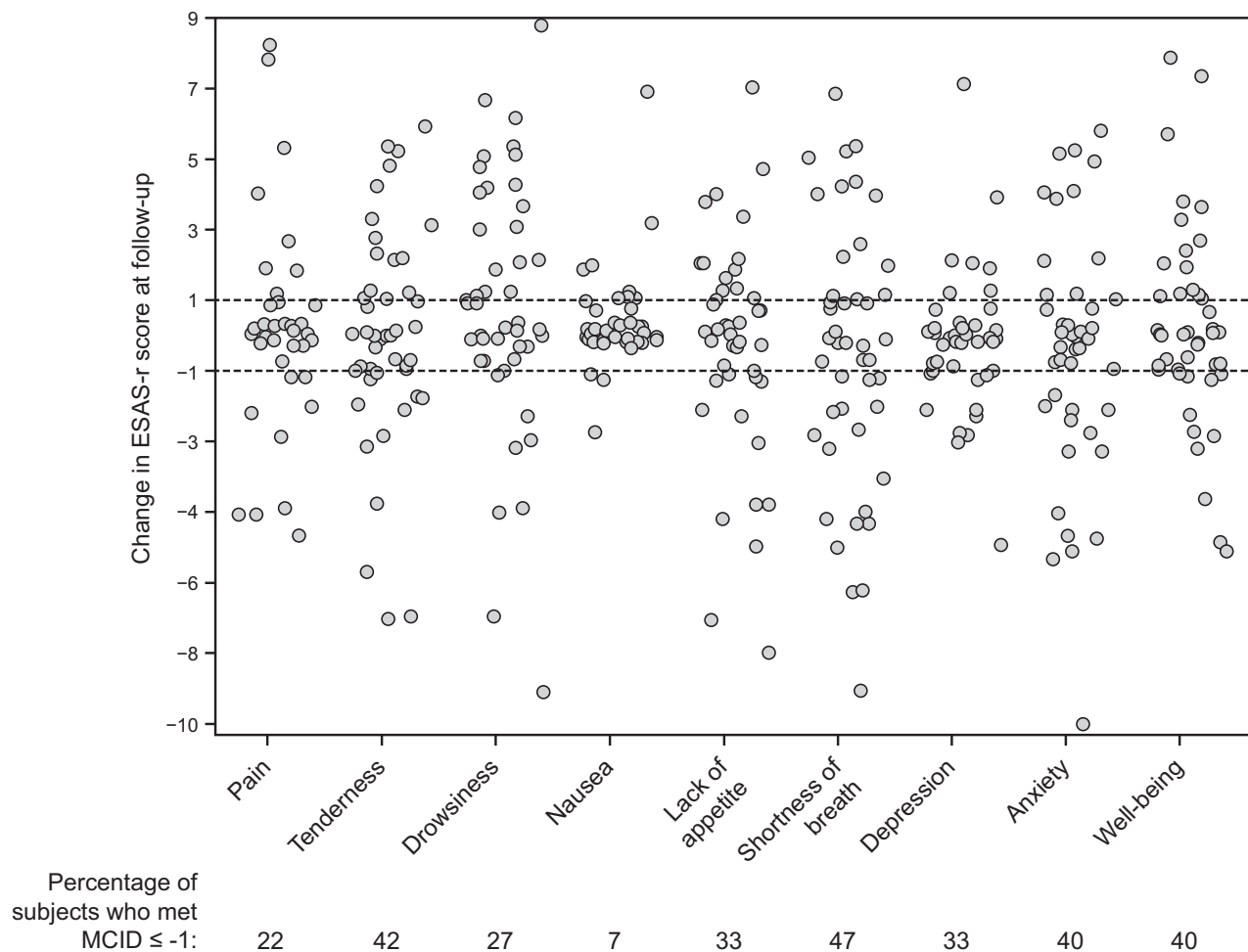


Fig. 3. Follow-up revised Edmonton Symptom Assessment System (ESAS-r) score in the 45 subjects with COPD. The values are individual data points of the differences between the baseline and the follow-up visit. The figure also shows the percentage of the subjects who met the minimum clinically important difference (MCID) of improvement of least -1 for each domain. Dotted lines denote minimum clinically important difference.

nual ED and/or hospital visits did not reach statistical significance. However, in a secondary analysis, 47% of the subjects were identified as responders (ie, met the minimum clinically important difference for improvement in the ESAS-r shortness of breath domain at follow-up) and 40% showed improvements in ESAS-r scores for anxiety and general well-being. In the subset of the subjects who reached the ESAS-r minimum clinically important difference for dyspnea domain, there was an additional reduction of the frequency of annual ED visits. As such, the responders had significantly less frequent (by 31%) ED visits compared with the nonresponders in the second year after their first visit to this clinic. Responders and nonresponders had similar baseline MRC dyspnea scores, clinical characteristics, baseline lung function, and comorbid conditions.

This specialized clinic was established to provide holistic care (total person care) that draws on integrated palliative care for patients who are severely breathless and

with chronic respiratory diseases. As per the results of a recent systematic review that included 37 articles that discussed holistic services for patients with advanced disease and chronic breathlessness, such services are usually offered to patients with thoracic cancer and are mostly short term (4–6 weeks).²³ Our intention was to provide support to patients with distressing breathlessness, especially in noncancer conditions, in which such service is not usually available. In our clinic, the patients were followed up for as long as they were in need or until they were no longer able to come to the clinic, and they were referred for ongoing follow up at home by their family physician or a community palliative care physician. Clinic visits lasted 30 to 60 min per patient. Family members and friends were encouraged to attend these clinics where there was ample opportunity for detailed discussions and planning. The clinic provided multiple services, including smoking cessation support, educational advice about the disease

INTEGRATIVE MANAGEMENT OF SEVERE BREATHLESSNESS IN COPD

Table 5. Comparison Between Patients With COPD: Responders and Nonresponders

Variable	Responders (n = 21)	Nonresponders (n = 24)	P
Demographics			
M:F, n	10:11	15:9	NA
Age, mean \pm SD y	69 \pm 7	72 \pm 7	.17
BMI, mean \pm SD kg/m ²	28 \pm 15	29 \pm 19	.96
MRC dyspnea score (1–5), mean \pm SD	4.78 \pm 0.43	4.71 \pm 0.46	.66
Baseline ESAS-r score for shortness of breath, mean \pm SD	4.86 \pm 2.63	1.50 \pm 2.04	<.001
Pulmonary function test			
mean \pm SD			
FEV ₁ , % predicted	37 \pm 21	34 \pm 16	.54
FVC, % predicted	69 \pm 16	64 \pm 18	.34
FEV ₁ /FVC, %	36 \pm 14	37 \pm 10	.66
Inspiratory capacity, % predicted	76 \pm 21	72 \pm 27	.63
FRC, % predicted	183 \pm 45	175 \pm 53	.59
TLC, % predicted	134 \pm 41	135 \pm 29	.93
RV, % predicted	231 \pm 76	219 \pm 78	.65
RV/TLC, %	61 \pm 13	63 \pm 11	.58
D _{LCO} , % predicted	51 \pm 31	49 \pm 16	.75
Comorbidities, n (%)			
Diabetes mellitus	0 (0)	5 (21)	.051
Systemic hypertension	8 (38)	9 (38)	>.99
Ischemic heart disease	3 (14)	3 (13)	>.99
Heart failure	2 (10)	5 (21)	.42
Extrapulmonary cancer	4 (19)	5 (21)	>.99
Obstructive sleep apnea	5 (24)	9 (38)	.34
Pulmonary hypertension	3 (14)	5 (21)	.71
Anxiety and/or depression	10 (48)	14 (58)	.56
Difference of the ESAS-r score between baseline and follow-up, mean \pm SD			
Pain	0.00 \pm 2.32	0.38 \pm 2.73	.63
Tiredness	−0.62 \pm 2.77	0.50 \pm 2.93	.20
Drowsiness	0.71 \pm 3.84	1.00 \pm 3.13	.79
Nausea	0.14 \pm 0.96	0.54 \pm 1.59	.32
Lack of appetite	−0.14 \pm 2.41	−0.08 \pm 3.19	.95
Shortness of breath	−3.17 \pm 2.11	2.17 \pm 2.08	<.001
Depression	0.19 \pm 1.97	−0.46 \pm 1.74	.25
Anxiety	−0.24 \pm 2.64	−0.42 \pm 3.57	.85
Well-being	−0.62 \pm 2.13	1.00 \pm 2.96	.044

NA = not applicable

BMI = body mass index

MRC = Medical Research Council

ESAS-r = revised version of the Edmonton Symptom Assessment System

FRC = functional residual capacity

TLC = total lung capacity

RV = residual volume

D_{LCO} = single-breath diffusing capacity of the lung for carbon monoxide

and its treatments, a review of inhaled therapy techniques, collaborative self-management plans, and sleep hygiene advice, all on an individualized basis.

Furthermore, based on the subjects' requirements, targeted pharmacologic interventions that mainly included opioids, methotrimeprazine, and oxygen therapy were also offered. Opiate therapy is the most studied class of pharmacologic agents for relieving refractory dyspnea across different disease states.^{24,25} Some studies demonstrated that the judicious use of oral opioids modestly but significantly improved dyspnea ratings, with only trivial insignificant worsening of pulmonary gas exchange (carbon dioxide level, arterial oxygen saturation),^{26–29} even in a frail older population.^{30,31} In our sample, most of those referred (89%) were prescribed oral opioids with the dose slowly up-titrated to decrease the severity of severe dyspnea experienced and with regular follow-up of their arterial blood gases. In addition, 31% of our subjects were prescribed methotrimeprazine to help with dominant respiratory-related anxiety and panic attacks. Given that the intervention (pharmacologic and non-pharmacologic) applied through this clinic was not offered in a stepwise manner (one intervention at a time), we could not assess the impact on breathlessness of each component in isolation.

A recent systematic review highlighted that only a small percentage of subjects with COPD had discussed the role of palliative care with their clinicians.³² Clinicians in busy pulmonology clinics do not facilitate satisfactory conversations that identify patients' preferences in the advanced phases of disease. Indeed, in the current study, end-of-life issues had not been previously discussed in the majority of referred patients before their enrollment in the advanced dyspnea clinic. Within this clinic, 82% of the subjects became engaged in end-of-life care discussions and goals of care preferences. Our results showed that this clinic not only provided new pharmacologic treatments for this patient population but provided other support, such as advance care planning, nutritional advice, referral to spiritual care or social work, and referral to community home-based palliative care services to promote continuity of care in the patient's choice of location. Collectively, these results demonstrated that such specialized clinics help mobilize additional resources and provide more comprehensive management in patients with severe refractory dyspnea than what can be offered in busy general pulmonology clinics.

Dyspnea is an intensely personal experience not easily captured numerically on various scales currently at our disposal. The expression of dyspnea is highly variable across individuals, with wide variation in precipitating events (eg, diurnal pattern, anxiety, physical activity, body position, sputum impaction, coughing spell). The affective dimensions of the symptom are also variable across individuals and must be considered if effective treatment is to be offered. Many of our subjects with refractory dyspnea had full-blown panic attacks

INTEGRATIVE MANAGEMENT OF SEVERE BREATHLESSNESS IN COPD

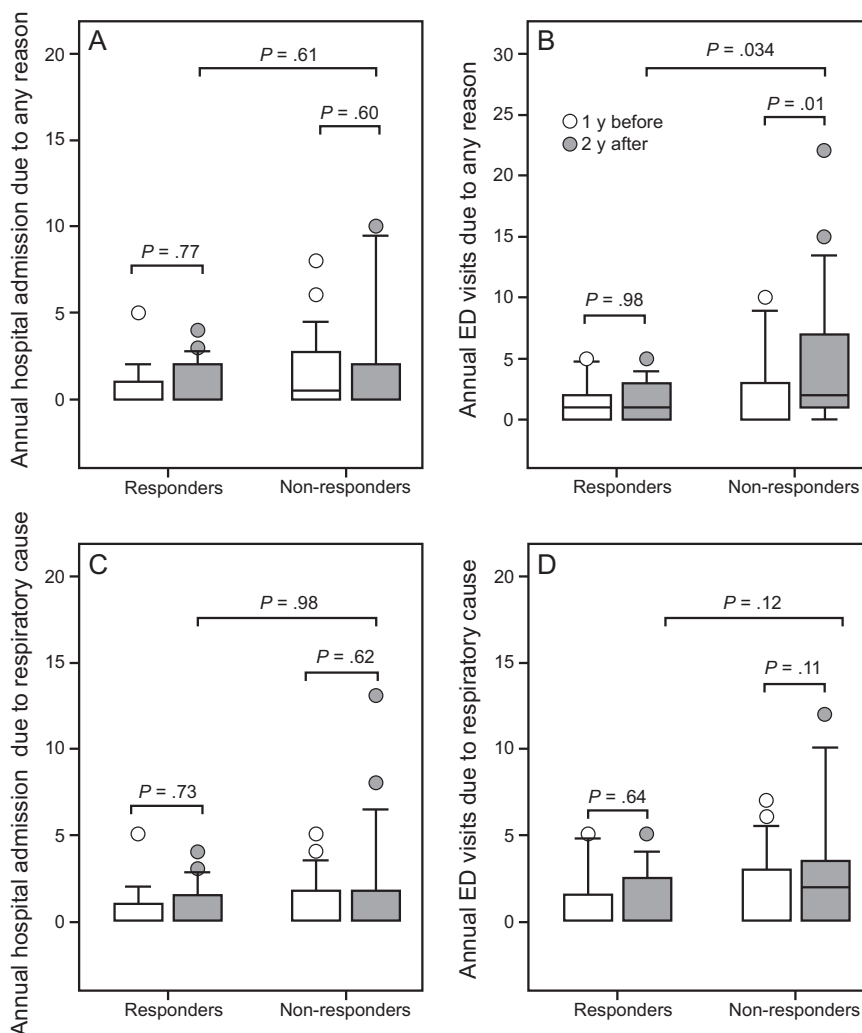


Fig. 4. Annual hospital admission and emergency department (ED) visits 1 year before and 2 years after the first clinic visit in subjects with COPD (responders and nonresponders) whether due to any reason (A and B) or due to respiratory cause (C and D). Responders are defined as those with at least a -1 change in ESAS-r score for the shortness of breath domain at follow-up. Boxes depict the first to third quartiles; center lines denote the median. Whiskers range from the 10th to the 90th percentile. The Wilcoxon rank-sum test was used for between-groups comparisons in the 2 years after the first clinic visit and Wilcoxon signed-rank test was used for pre-post comparisons with each group. ESAS-r = revised Edmonton Symptom Assessment System.

related to breathing discomfort, and, in some, these could escalate to “dyspnea crisis,” which precipitated emergency admissions to the hospital. In the clinic, comprehensive questioning and exploration of each individual’s dyspnea experience was undertaken, and, accordingly, personalized targeted management strategies were initiated (Fig. 1). Anecdotally, this approach was successful in most subjects who reported consistent subjective benefit. Unfortunately, important personal qualitative benefits were underestimated when using the minimum clinically important difference from the dyspnea component of the ESAS-r scale. More-refined assessments of symptom improvement that focus on the response of individuals to structured interventions are clearly needed.

Limitations

This was a retrospective study and lacked a control arm to more definitively determine the causal impact of a specialized clinic and its individual components in caring for patients with refractory dyspnea. Furthermore, the small sample size and single-center design may limit the generalizability of results. The small sample size might also be responsible for the lack of possible differences in baseline clinical characteristics of the responder and nonresponder groups. Nevertheless, this preliminary analysis provided important information that will allow refinements in study design for future studies in this neglected population. The interval between follow-up visits was not consistent; this

INTEGRATIVE MANAGEMENT OF SEVERE BREATHLESSNESS IN COPD

affected our analysis of responders versus nonresponders and allowed us to only look at the short-term response for this study in a subset of subjects. The ESAS-r is a validated instrument mainly used to assess the change in severity of symptoms over time and the response to therapeutic interventions in patients with cancer. The wide disparity between assessments of dyspnea by using the MRC scale, which indicated disabling dyspnea (an inclusion criterion), and the ESAS-r shortness of breath score, which, in some individuals indicated only minor shortness of breath, indicated that the latter may not be the best tool to assess symptoms and response to treatment in patients with chronic respiratory disease.

Conclusions

Our study provides new insights into the role of a specialized advanced dyspnea clinic in improving dyspnea and other patient-centered outcomes in subjects with advanced COPD, who, unfortunately, are destined to progressively deteriorate over time. The study showed that a specialized clinic provided short-term, clinically meaningful improvements in dyspnea and other subjective outcomes, with significant reduction in hospital emergency visits in a good proportion of the sample. Our preliminary study set the stage for new randomized controlled studies to evaluate the efficacy and, it is hoped, provide further justification for specialized clinics for the palliative care management of refractory dyspnea in persons with advanced respiratory diseases.

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