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Depression and its relationship with poor exercise capacity, BODE index and muscle wasting in COPD

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Summary

Background: The prevalence of depression in stable COPD patients varies markedly, possibly because of use of different scales. We aimed to assess depression using 2 different depression scales and to examine the association between depression and poor exercise performance, BODE index and muscle wasting in clinically stable COPD patients.

Methods: 122 stable COPD patients were assessed with the Centre for Epidemiologic Studies Depression Scale (CES-D) and the Brief Assessment Schedule Depression Cards (BASDEC). We also assessed patients with spirometry, bioelectrical impedance analysis, 6-minute walk distance (6MWD), St George's Respiratory Questionnaire (SGRQ) and MRC dyspnoea and Borg scales.

Results: The CES-D and BASDEC scales detected almost similar prevalence rates of depression (21% vs 17%) with a Kappa coefficient of 0.68, $p < 0.0001$. The BASDEC scale detected more depression in women and was more closely associated with dyspnoea than the CES-D. COPD severity was associated with depression when using BODE scores but not when GOLD categories were used. Each of the CES-D and BASDEC depression scores were associated with 6MWD after adjusting for FEV₁% predicted, gender, age and pack-years ($p = <0.0001$ and 0.001, respectively). Also, patients with a 6MWD < 350 scored significantly higher on both depression scales. Wasted patients appeared to have higher depression scores, but the difference was statistically insignificant.

Abbreviations: BMI, Body Mass Index; BODE, Multidimensional index (B = Body mass index, O = Obstruction of airways as measured by FEV₁, D = Dyspnoea as measured by MRC scale, E = Exercise capacity as measured by 6MWT); BASDEC, Brief Assessment Schedule Depression Cards; CES-D, Centre for Epidemiologic Studies Depression; COPD, Chronic obstructive pulmonary disease; FFMI, Fat-Free Mass Index; FEV₁, Forced Expiratory Volume in 1 Second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IQR, Interquartile range; kPa, kilo Pascal; L, Litre; MRC scale, Medical Research Council Scale; 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; m, Meter; OR, Odds ratio; PaCO₂, Arterial carbon dioxide pressure; PaO₂, Arterial oxygen partial pressure; Q, Quartile; SGRQ, St George's Respiratory Questionnaire.

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Conclusion: The administration of different depression scales may affect some of the characteristics of depressed patients rather than the prevalence rate of depression. Depression was associated with poor exercise performance and BODE index in COPD.

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Introduction

Chronic obstructive pulmonary disease (COPD) is an incurable disease causing major disability, morbidity, and mortality.^{1,2} The pulmonary and extrapulmonary manifestations of COPD seriously affect patients' physical, social and emotional states.^{1,3} It is therefore not surprising to find a higher prevalence of depression in COPD patients than in either healthy controls^{4,5} or even patients with other chronic illnesses such as Parkinson's disease, stroke, arthritis and tuberculosis.^{5,6}

The prevalence of depression in COPD patients has varied significantly from 6 to 74%.^{7–14} This variation has been explained mainly by differences in COPD severity, assessment tools or patients' characteristics.^{3,8} Importantly, the actual assessment tools being used may influence the final result as depression assessment scales differ in their design, method of administration, number of items and cut-off points. This may result in different depression prevalence rates and variations in the relationships between depression and the demographic characteristics of the sample populations.

Depression may affect exercise capacity in COPD. The area is not well studied although a limited number of studies have found no relationship.^{5,15}

There is generally a growing understanding of the multisystem effects of COPD¹ and currently the BODE index (B = Body mass index, O = Obstruction of airways as measured by FEV₁, D = Dyspnoea as measured by MRC scale, E = Exercise capacity as measured by 6MWT) is widely accepted as a multidimensional assessment tool.¹⁶ Several studies have reported a good association of BODE scores with impairment in quality of life,¹⁷ limited physical activity¹⁸ and higher mortality.¹⁹ Depression is one of the major comorbidities of COPD which is associated with exacerbations,²⁰ poor prognostic outcome²¹ and mortality.²² For this reason, the relationship of depression with BODE index deserves investigation.

Low body mass index (BMI) is an independent prognostic factor for mortality in COPD.²³ Chavannes et al. found a negative association between overweight (body mass index (BMI) > 25) and depression (OR 0.4, 95% CI 0.2–0.8).¹⁰ A recent study showed that low fat-free mass index (FFMI = Fat-free mass/height² (kg/m²)) is a significant predictor of overall mortality, even in patients with normal BMI.²⁴ However, the association between the presence of depressive symptoms and body weight and particularly metabolically active tissues (fat-free mass) is poorly understood and needs further study.

We examined the prevalence rate of depression in patients with clinically stable COPD and whether it differed according to the two different tools. We also assessed the effect of using different depression scales on the correlation between depression and the patients' demographic

characteristics. We explored the association between depression and poor exercise performance, BODE index and muscle wasting in patients with stable COPD.

Methods

Study subjects

Subjects were recruited from media advertising, a Medicines Evaluation Unit, and the outpatient chest clinic at the North West Lung Centre, South Manchester University Hospital Trust, Manchester. COPD was diagnosed according to GOLD guidelines²⁵; all patients had to be clinically stable at least 4 weeks before the time of the visit (Fig. 1). Patients were excluded if they had current or recurrent symptomatic ischemic heart disease, lung cancer, known psychiatric illness, maintenance treatment with systemic corticosteroids, active tuberculosis or insulin-dependent diabetes mellitus. Patient recruitment extended from April 2006 to December 2007.

Prior to the visit patients were instructed to fast for 4 h and withhold their short-acting bronchodilators for 6 h, all other inhalers for 12 h, and to avoid alcohol and strenuous exercise for 24 h. All participants gave written informed consent. The Tameside and Glossop Local Research Ethics Committee in Manchester approved the study.

Assessments

Bioelectrical Impedance Analysis (BIA) was performed in the supine position at the beginning of the visit using Bodystat 1500 (Bodystat Ltd, Douglas, UK). For defining muscle-wasting, we used previously published Dutch criteria; fat-free mass index (FFMI) < 16 kg/m² for men and FFMI < 15 kg/m² for women.²⁶

Spirometry was done according to the ATS/ERS Standardization Guideline²⁷ using a Jaeger MasterScreen spirometer (Jaeger Ltd, Hoechberg, Germany). Earlobe capillary blood gases were measured according to the method described by Spiro and Dowdeswell²⁸ using a Radiometer analyzer (Radiometer Medical A/S, Copenhagen, Denmark).

Exercise capacity was measured using the 6-minute walk test (6MWT) according to the ATS guideline.²⁹ Before and after completion of the 6MWT, dyspnoea and fatigue were assessed using Borg scale³⁰ and pulse rate and oxygen saturation (Nonin Oximetry, Plymouth, USA) were measured.

Health Status was measured by the St George's Respiratory Questionnaire (SGRQ).³¹ Dyspnoea was assessed using the MRC dyspnoea scale.³² The multidimensional (BODE) index was also used.¹⁶ For assessment of depression two instruments were used: The Brief Assessment Schedule

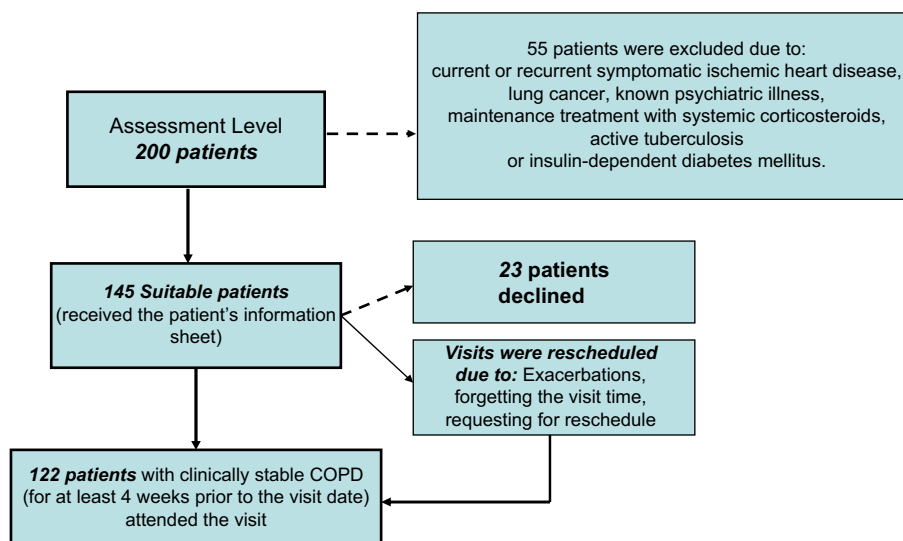


Figure 1 Flow chart illustrating participant eligibility, exclusion and enrolment.

Depression Cards (BASDEC) and the Centre for Epidemiological Study on Depression (CES-D) Scale. BASDEC has been used effectively in clinical assessment of depression³³ in COPD patients and other elderly patients^{9,33,34}; it utilizes the response at the bedside to each of its 19 cards with 'true', 'false' or 'I do not know'. Two items are scored with two points and the maximum score is 21. A score of seven or above indicates possible case for depression. CES-D is a reliable self-administered questionnaire³⁵ and extensively used in assessing depressive symptoms in elderly healthy and ill populations. It consists of 20 negative and positive items, and scores range from 0 to 60 and a score of 16 or higher indicates the presence of depressive symptoms. To avoid overlap and biased response, CES-D was introduced after body composition measurement and the BASDEC after lung function tests.

Statistical analysis

We used the chi-squared (χ^2) test and the independent sample *t*-test (unless otherwise noted) for descriptive analyses. A kappa coefficient was calculated to examine the agreement between depression scales. Binary logistic regression was used to assess sensitivity, specificity and positive/negative predictive values of BASDEC against CES-D. Non-parametric data were natural log transformed or presented as median and interquartile range (IQR). We used χ^2 test to investigate the categorical association between depression and COPD severity as represented by GOLD stages and BODE quartiles as published in the original study by Celli et al.¹⁶

To examine the correlation between depression scores and 6-minute walk distance (6MWD) and health status univariate and multivariate analyses were performed using either 6MWD or natural log transformed BASDEC or CES-D scores as the dependent variable in COPD subjects. Binary logistic regression was also used to investigate the association between exercise performance as a categorical variable (cut-off of 350 m from the 6MWD) and depression, adjusting for lung function (FEV₁% predicted, PaO₂ and

PaCO₂). We used χ^2 test to examine the categorical association of walking distance (<350 m vs \geq 350 m) with depression (depressed vs not depressed) and MRC grades (grades 1,2,3 vs 4,5). The association of depression with body mass and fat-free mass was examined using the χ^2 and independent sample *t*-tests. Significance was defined at *p*-value \leq 0.05. SPSS version 14 (SPSS Inc, USA) was used.

Results

Patients' characteristics

From 145 eligible patients, a total of 122 patients with stable COPD were recruited. The mean age was 66 years and women made up 39% of the sample; other characteristics are shown in Table 1. The median BODE score was 2 with 6% of patients having a BODE score of 7 or more. Men were older, had worse lung function and higher fat-free mass index than women. Despite a higher cumulative tobacco exposure more men than women had stopped smoking (Table 1).

The prevalence of depression

According to the CES-D questionnaire 21% had depressive symptoms and 17% were depressed according to the BASDEC scoring system. Using depression defined by either one of the questionnaires the prevalence of depression increased slightly to 23.4%.

Table 2 shows that more women were depressed using the BASDEC, but not the CES-D. In addition, BASDEC was more sensitive than CES-D in detecting an association between MRC dyspnoea grade and depression as shown in Table 2. There was a good overall agreement between the two questionnaires (kappa = 0.68, *p* < 0.0001). Against CES-D, BASDEC showed a high specificity 90.8% but lower sensitivity 82.6%, a negative predictive value of 95.7% and a positive predictive value of 68%.

Table 1 Baseline characteristics of the sample; mean values and standard deviations are shown unless otherwise noted.

	All	Men	Women	p-Value
Number	122	75	47	
Age, yrs	66 ± 6.7	67 ± 6.4	64 ± 7	0.03
Ex/current smokers	87/35	56/19	31/16	0.37
Pack/years median (IQR)	40 (25.8)	43.8 (30.4)	36 (19)	0.06 ^a
FEV ₁ %	52.5 ± 18.5	48.9 ± 17.7	56.6 ± 18.7	0.03
FEV ₁ /FVC	45.8 ± 13.6	43 ± 12.8	50.4 ± 13.2	0.004
PaO ₂ (kPa)	9.2 ± 1.4	9 ± 1	9.4 ± 1.4	0.07
PaCO ₂ (kPa)	5.2 ± 0.58	5.2 ± 0.6	5.1 ± 0.6	0.25
BMI (kg/m ²)	27.5 ± 5.8	27.4 ± 6	27.8 ± 5.9	0.77
FFMI (kg/m ²)	17.8 ± 3.1	19.1 ± 3	16.2 ± 3.1	<0.0001
GOLD 1	6 (5%)	3	3	0.2 ^b
GOLD 2	61 (50%)	34	27	0.2 ^b
GOLD 3	39 (32%)	26	13	0.2 ^b
GOLD 4	16 (13%)	12	4	0.2 ^b
SGRQ total score	46 ± 20	45.6 ± 21	47.9 ± 19	0.55

IQR = Interquartile Range; FEV₁% = Forced Expiratory Volume over 1 second of predicted; FVC = Forced Vital Capacity; PaO₂ = Arterial oxygen partial pressure; kPa = kilo Pascal; PaCO₂ = Arterial carbon dioxide pressure; BMI = Body Mass Index; FFMI = Fat-Free Mass Index; GOLD = Global Initiative for Chronic Obstructive Lung Disease; and SGRQ = St George's Respiratory Questionnaire.

^a Mann-Whitney *U* Test.

^b χ^2 -Test between all GOLD stages in males and females.

Depression and exercise capacity

There was a significant correlation between BASDEC and CES-D scores and 6-minute walk distance (6MWD), rho 0.33 and 0.4, respectively, $p < 0.001$ for both. Two separate modules of multivariate analyses showed that each of the CES-D and BASDEC depression scores was independently associated with 6MWD after adjusting for FEV₁% predicted, gender, age and pack-years ($p \leq 0.0001$ and

0.001, respectively). Using categorical variables, patients without depression performed better in the 6MWT than depressed patients (Table 2). Using the 6MWD cut-off point of 350 m (as in the BODE score) patients who walked ≥ 350 m had significantly lower depression scores than those walking < 350 m (Table 3). Logistic regression analyses using 350 m as cut-off point was performed to assess the impact of depression on exercise capacity after adjusting for FEV₁, PaO₂ and PaCO₂. In both models

Table 2 Differences between patients with and without depression; mean values and standard deviations are shown if nothing else is noted.

	All	CES-D scale		<i>p</i>	BASDEC scale		<i>p</i>
		Depressed	Not depressed		Depressed	Not depressed	
Total	122	29	93		23	98	
Gender (men/women)	75/47	15/14	60/33	0.31	9/14	65/33	0.03
Age (years)	66 ± 6.7	63.7 ± 7.8	66.9 ± 6.4	0.05	62.8 ± 7.1	66.7 ± 6.4	0.02
Age ≥ 65 / < 65	77/45	13/16	64/29	0.03	10/13	66/32	0.056
FEV ₁ %	52.2 ± 18.4	50.4 ± 16.4	52.4 ± 19.1	0.59	50.1 ± 15	52.3 ± 19.2	0.56
FVC (L)	3 ± .9	2.8 ± 0.8	3 ± .9	0.16	2.7 ± .8	3 ± .9	0.06
BMI (kg/m ²)	27.5 (5.8)	28.7 ± 6.5	27.2 ± 5.5	0.2	29 ± 6.7	27.2 ± 5.6	0.2
FFMI (kg/m ²)	17.9 (3.3)	17.76 ± 3.4	18 ± 3.3	0.7	18 ± 3.3	17.6 ± 3.7	0.6
6MWD (m)	353.7 ± 69	325.6 ± 65.4	354.6 ± 73	0.05	313.7 ± 61.1	355 ± 72.9	0.01
Dyspnoea (Borg scale) after 6MWT (median (IQR))	3 (3)	3 (1.5)	2 (2.4)	0.008 ^a	3 (2)	2 (2.5)	0.004 ^a
Fatigue (Borg scale) after 6MWT (median (IQR))	2 (3.5)	3 (3)	2 (2.5)	0.002 ^a	3 (3)	2 (2.5)	<0.0001 ^a
MRC dyspnoea scale (median (IQR))	1 (1)	2 (2)	1 (1)	0.07 ^a	2 (2)	1 (1)	0.02 ^a
SGRQ total score	46 ± 20	63.8 ± 16.1	41.1 ± 18.3	<0.0001	66.4 ± 13.8	41.9 ± 19	<0.0001

p = *p*-Value; CES-D = Centre for Epidemiologic Studies Depression Scale; BASDEC = Brief Assessment Schedule Depression Cards; FEV₁% = Forced Expiratory Volume over 1 second of predicted; FFMI = Fat-Free Mass Index; FVC = Forced Vital Capacity, 6MWD = 6-Minute walk distance, m = meter; IQR = Interquartile Range; and SGRQ = St George's Respiratory Questionnaire.

^a Mann-Whitney *U* Test.

Table 3 Depression scores in groups according to exercise capacity; median values and interquartile range are shown

	6MWD \geq 350 m	6MWD $<$ 350 m	<i>p</i>
CES-D score	6 (9)	12 (12)	<0.0001
BASDEC score	2 (4)	4.5 (5)	<0.0001

CES-D = Centre for Epidemiologic Studies Depression Scale; BASDEC = Brief Assessment Schedule Depression Cards; 6MWD = 6-Minute walk distance; m = meter; and *p* = *p*-value.

depression based on either the CES-D or BASDEC scales was a significant predictor of poor exercise performance, OR 1.11 (95% confidence interval 1.05–1.18, $p < 0.001$) and OR 1.25 (1.08–1.42, $p = 0.001$), respectively. Moreover, in our 59 patients who walked < 350 m in 6MWT we found only 15 with severely breathlessness (MRC grades 4,5), whereas 18 were depressed (using the BASDEC scale), and only 6 (33%) of those 18 depressed patients had MRC grades 4 or 5. Similarly, when using the CES-D scale, we found that 20 patients (out of 59) were depressed and only 8 of those depressed patients had MRC grades 4,5.

Depression and BODE score

Spearman correlation showed a significant association between scores of both depression scales (CES-D, BASDEC) and total BODE scores ($\rho = 0.35$, $p < 0.001$ and $\rho = 0.22$, $p = 0.016$, respectively) but not FEV₁%. Using the BODE quartiles (Q1–4), patients with the most severe disease (Qs 3&4) were more likely to suffer from depression (using CES-D) than those with milder disease (Qs 1&2), odds ratio (OR) = 4.0 (1.5–10.6, $p = 0.007$). A similar association was seen for the BASDEC score, OR = 3.8 (1.4–10.4, $p = 0.02$). This association between severity of COPD and depression was not seen when using GOLD stages (combined stages 3&4 compared to combined stages 1&2), neither for the CES-D scale (OR = 1.2

(0.5–2.7, $p = 0.9$)), nor the BASDEC scale (OR = 1.1 (0.45–2.8, $p = 0.98$)).

Depression and body composition

We found that 24% of our sample had muscle-wasting and 12% had a BMI < 21 . Amongst the depressed patients, we found that seven had muscle-wasting but only one patient had a BMI < 21 .

There was no significant association between BMI and depression. Similarly, when using the cut-off value of either BMI > 25 or < 21 no significant difference in rates of depression (as continuous or categorical variable) were detected. There was a tendency to patients with muscle-wasting having higher depression scores than those without wasting but the differences were statistically insignificant (median BASDEC score 4 vs 2.5, $p = 0.16$ and median CES-D score 11 vs 9, $p = 0.4$).

Depression and health status

Poor health status was significantly associated with depression using either depression scale ($p = < 0.0001$) (Fig. 2). This association remained unchanged after taking FEV₁% predicted, BODE score, smoking status, dyspnoea and fatigue scores in Borg Scale (after 6MWT) into account ($p = < 0.0001$). Depression alone (using either of the scales) explained 31% of the health status and in the previous adjusted model BASDEC explained 57% and CES-D 53% of the variation in health status. Moreover, we found that impairment of health status (total SGRQ score) was more pronounced in depressed patients (using either CES-D or BASDEC) than in patients who had MRC grades 4 or 5 (64, 66 and 61, $p < 0.001$, respectively).

Discussion

We found a significant prevalence of depression in mainly moderate clinically stable COPD which was approximately

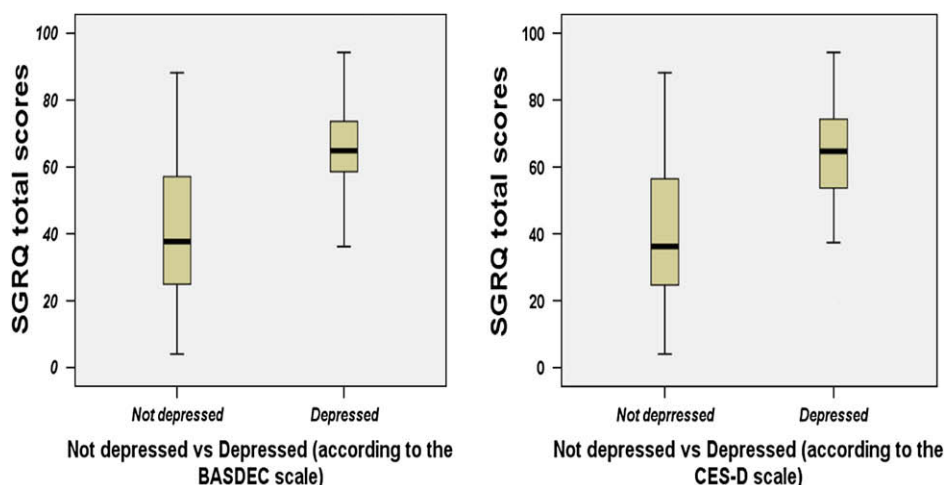


Figure 2 Boxplot of the median (IQR) of the SGRQ total scores for depressed and not depressed according to either BASDEC or CES-D scales. The end of the whiskers represent the maximum and minimum of SGRQ scores. IQR = Interquartile range; SGRQ = St George's Respiratory Questionnaire; BASDEC = Brief Assessment Schedule Depression Cards; CES-D = Centre for Epidemiologic Studies Depression Scale.

similar when using two different scales. Depression was significantly associated with limited exercise capacity and the BODE index. Depressed patients had lower muscle mass than not depressed but the difference was statistically insignificant.

The prevalence of depression and the sample characteristics

We found that depression is a common condition in clinically stable COPD and its high prevalence changed only slightly when using different scales. This finding does not lend support to the suggestion that the employment of different scales may affect the actual prevalence of depression in COPD.³ We used the CES-D and BASDEC depression screening scales and they are different in their design, items number, scoring systems and administration methods. The CES-D scale led to a slightly higher prevalence rate of depression than BASDEC (21 vs 17%); however, both figures were consistent with other studies in which 20 (± 5)% of patients were depressed.^{3,4,12}

Whereas the prevalence seems independent of the questionnaire used, the use of different scales may affect the association between gender and depression. In our study only BASDEC showed that women were more depressed than men. Three other studies have reported similar findings.^{4,10,13} However, Cleland et al. used the Hospital Anxiety and Depression Scale (HADS) and found no association between gender and depression.¹² This could be due to questions in some of the screening tools relating more to issues in depression such as sadness, being more psycho-biologically related to women as suggested by Salokangas et al.³⁶ We found that depressed patients were younger than those not depressed. Consistently, Cleland et al. suggested that the burden of COPD on younger patients seems higher as they may need to change life style, retire early or find easier jobs¹² whereas older patients may accommodate more easily and ascribe some of their limitations to the consequence of ageing.³⁷

Clinical implication

The employment of a simple tool to assess depression is important as depressed patients may not present their depressive symptoms in a straightforward fashion. Unscreened and consequently unmanaged depression may result in further deterioration since depression is significantly associated with exacerbations,²⁰ relapse and frequent admissions,²¹ and higher mortality.²² This may result in increased consumption of primary and secondary health care resources.

Administration of the BASDEC took less time than the CES-D, and as in a previous study the patients responded friendly to its cards.³³ In addition, it was much easier and quicker to score than the CES-D. It therefore seems suitable for employment in busy clinics. Moreover, the BASDEC covered uniquely serious complaints such as suicidal ideas. It seems intuitively important to screen for the presence of suicidal thoughts in older people,³⁸ particularly if we consider the multidimensional persistent burden of COPD.

Depression, exercise capacity and quality of life

In our study depression was associated with poor exercise capacity independent of our choice of depression screening tool. Previously, Light et al. and Yohannes and colleagues did not find a significant association between depression and limitation in exercise capacity. In their study Light et al. examined 45 men¹⁵ and Yohannes et al. studied only elderly COPD patients with short walking distances.⁵ In addition to looking at association of depression with distance walked we also examined a 6MWD threshold of 350 m, the distance used as cut-off value in the BODE score,¹⁶ and recently considered by Cote et al. as a marker of poor exercise performance.³⁹ Our study showed that patients with limited exercise capacity had significantly higher scores on both depression scales (Table 3). Also, our logistic regression model showed that poor exercise performance was affected by depression but not by the deterioration in lung function. In addition, we found that only a third of depressed patients with poor exercise performance would have been identified using severe breathlessness with the MRC scale (grades 4 and 5).

Impairment of quality of life is associated with both depression²⁰ and breathlessness.⁴⁰ International guidelines have advised that patients with higher MRC grades (usually 3–5) should be offered pulmonary rehabilitation.^{41,42} We found that a substantial part of health status impairment was explained by depression which had at least the same impact on quality of life as severe dyspnoea (MRC grades 4,5). Thus, earlier detection of depression, treatment and pulmonary rehabilitation may be very important. Studies have showed improvement in depression after pulmonary rehabilitation^{43,44} and some have indicated that intervention with anti-depressant medications may improve exercise capacity^{45,46} and quality of life.⁴⁵

Depression and BODE index

Similar to many other studies we found no association between level of FEV₁ and depression scores.^{4,10,15} Whereas depression did not differ with GOLD stages, the multidimensional BODE index was associated with depression. To the best of our knowledge, this is the first study showing a relationship between depression and BODE index. BODE index is a multidimensional tool assessing uniquely the multisystem effects of COPD.¹⁶ The association of low mood with BODE may reflect the overall effects of the many aspects of COPD and underlines the multisystem nature of COPD and the limitations of relying on FEV₁ only when grading COPD.

Depression and body composition

In contrast to the findings of Chavannes et al.¹⁰ but consistent with others^{4,5} we found no association between BMI and depression. Our data suggested that depression was more closely associated with depletion in the lean mass than the whole body mass but these findings were not statistically significant. Depression may lead to poor appetite and limited mobility; all contributing to loss of

fat-free mass^{47,48} which may subsequently lead to poor exercise capacity.⁴⁹

Our study was a cross-sectional study and cannot explain mechanisms sufficiently as cause–effect relationships require longitudinal studies. However, our sample size was fairly large with a balanced gender distribution and uni-ethnicity (Caucasians), and our methodology was structured and our tools validated. Additionally, all the data were collected on clinically stable patients on visits to our centre.

Conclusion

In conclusion, we found a significant rate of depression in COPD patients with mainly moderate clinically stable disease which was only slightly affected by using different tools for assessing depression. Depressed patients had poor exercise performance and worse health status. Depression was associated with BODE index, a significant predictor of subsequent mortality in COPD. Thus, there is a need for early identification and management of depression in patients with COPD.

Statement of disclosure

Author Khaled Al-shair has no financial or other potential conflicts of interest to disclose.

Author Rachel Dockry has no financial or other potential conflicts of interest to disclose.

Author Brendan Mallia-Milanes has no financial or other potential conflicts of interest to disclose.

Author Umme Kolsum has no financial or other potential conflicts of interest to disclose.

Author Dave Singh has no financial or other potential conflicts of interest to disclose.

Author Jørgen Vestbo has no financial or other potential conflicts of interest to disclose.

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