RESEARCH ARTICLE

DEPRESSION IN COPD: RISK DETERMINANTS AND HEALTH RELATED QUALITY OF LIFE (HRQOL)

*,[1]Kapil Sharma, [1]DPS Sudan, [1]Sheena Taneja, [2]Abhishek Kapoor, [3]Ashok Kumar Shah, [2]Rahul Rai and [1]Shweta Chauhan

[1]Department of Pulmonary Medicine, SGT Medical College & Hospital, Gurgaon, Haryana, India
[2]Department of Psychiatry, SGT Medical College & Hospital, Gurgaon, Haryana, India
[3]Department of Biochemistry, SGT Medical College & Hospital, Gurgaon, Haryana, India

ARTICLE INFO

ABSTRACT

Background & Objectives: Presence of two comorbidities, both chronic obstructive pulmonary disease (COPD) and depression impacts significantly on the morbidity and mortality of patients and thus interfering with quality of life and disease management. Indian studies throw limited light and data regarding identification of risk factors for depressive symptoms in patients with COPD and its impact on quality of life. This study was undertaken to identify the prevalence of depression and risk determinants of COPD patients attending a tertiary care health facility in north India.

Materials & Methods: COPD was classified according to GOLD stages based on forced expiratory volume in one second (FEV1) in 85 stable patients. Depression was examined by administering HAM-D (Hamilton depression) Scale. Linear regression model was used to examine association between predictor variables of COPD and depression with adjustment of age, sex and smoking status.

Results: In the study population as whole 51.76%, patients showed depressive symptoms. Higher depression scores 12.35 ± 9.18 was present in moderate to severe COPD. Depression was found to be higher among patients with higher CAT Score, SGRQ_S Score, SGRQ_I Score and SF-36-MCS scale (HRQoL) Score. Activity components of SGRQ (SGRQ_A Score) were found to be potential predictors of depression in COPD patients.

Interpretation & Conclusions: Majority of COPD patients have severe symptoms related to depression with increasing severity of COPD. Hence, clinicians and the patients both should be focused in adequate and timely management of both these comorbidities. Future studies are needed to adequately identify the casual association and management of both these conditions.

INTRODUCTION

The commonest mental health problem generally observed in our society which leads to higher level of functional impairment and emotional distress is depression (Ayuso-Mateos *et al*., 2001). Chronic obstructive pulmonary disease (COPD) is worldwide the fourth leading cause of morbidity and if the spreading epidemic of COPD continues the same way then it is expected to be the third leading cause of mortality by 2020 (Mannino and Kiriz, 2006). Worldwide, many studies have been conducted which finds a high prevalence of depression in patients presenting with an acute exacerbation of COPD ranging from 19.4% to 50% (Lacasse *et al*., 2001). Study conducted by Kunik *et al* suggested that anxiety and depression appears together in patients with COPD when compared with controls and the risk of depression is high in patients with

severe COPD (Kunik *et al*., 2005; van Manen *et al*., 2002). Overall there are two major depressive symptoms which includes depressed mood and loss of interest or pleasure in routine day today life. Additionally, depression include symptoms of early fatigue, low concentration, pessimism about the future, weight loss or gain, altered appetite, disturbed sleep, feeling of guilt, social isolation attitude and risk of suicidal tendencies. In addition, depressive COPD subjects suffer from impaired performance of daily today activities, impaired self-management of disease exacerbations, poor health behaviors, poorer self-reported health (Dowson *et al*., 2004; Johnson *et al*., 2005). Depression in patients with COPD is often undiagnosed and remains untreated which imposes an increased risk of exacerbation and hospitalization (Xu *et al*., 2008), imposes greater impact on functional impairment and physical disability (Katz *et al*., 2010). Symptoms of depression leads to social isolation, poor compliance with medical treatment and elevated risk of premature mortality (Yohannes, 2008; Dalal *et al*., 2011). Health-related quality-of-life

*Corresponding author: **Kapil Sharma,**
Department of Pulmonary Medicine, SGT Medical College & Hospital, Gurgaon, Haryana, India.

(HRQoL), as measured by the disease (COPD) specific St George's Respiratory Questionnaire (SGRQ) and SF-36 Generic health related quality of life (HRQoL) scale is linked both to respiratory and all-cause mortality (Oga *et al.*, 2003; Domingo-Salvany *et al.*, 2002). The multidimensional concept of HRQoL refers to the quality of life that is directly related to health or illness. Usually it includes the domains of illness related to the physical, social, and psychological impact. The patient's experience of illness can be defined as the subjective perception of the impact of health status on satisfaction with daily life (Barnes and Celli, 2009; Ozkaya *et al.*, 2011). Major depressive disorder has a direct impact on global disease burden accounting for 8.2% of years living with disability in 2010, noted by Ferrari *et al.* (2013). Depression is strong predictor for mortality in COPD patients with odds ratios 1.9-2.7 (Ng *et al.*, 2007). During the past few decades, researchers are more interested in knowing the multiple comorbidities associated with chronic obstructive pulmonary disease (COPD). Of such comorbidities, anxiety and depression contributes to substantial burden of COPD-related morbidity, mainly due to increased functional impairment, disability, decreased quality of life (Yohannes *et al.*, 2006; Hanania *et al.*, 2011; Cully *et al.*, 2006) and decreased treatment adherence (Kosmas *et al.*, 2014). Interestingly, patients with COPD and comorbid depression often prefer psychosocial over pharmacological treatments (Skultety and Zeiss, 2006). Depression is challenging to identify and treat because of overlapping symptoms with those of COPD.

Therefore, it is crucial to identify and appropriately develop treatment strategies for depression for improving the quality of life of COPD patients and thus reducing their healthcare utilization. Therefore, we conducted a study to estimate the prevalence of depression in patients with COPD visiting a tertiary health care centre in north India. Further, the association of depression with demographic and clinical characteristics of COPD patients was also measured.

MATERIALS AND METHODS

Study design

We conducted a cross-sectional, nonrandomized study in SGT Medical College & Hospital, Budhera, Gurgaon between October 2016 to April 2017. Adults (>40 years) with diagnosis of COPD attending the Chest Outpatient Clinic, who met the inclusion criteria, were screened for the study. The diagnosis of COPD was established based on complete medical history, symptoms, signs and available pulmonary function tests, as per the definitions provided by American Thoracic Society and European Respiratory Society. The study was approved by the Institutional ethics committee and written informed consent was obtained from all patients.

Inclusion and exclusion criteria

Inclusion criteria were (1) post bronchodilator(400 microgram Salbutamol) ratio of Forced Expiratory Volume in one second to Forced Vital Capacity less than 0.70 ($FEV_1/FVC<0.70$) (Global Initiative for Chronic Obstructive Lung Disease, 2016), (2) Stable conditions i.e. absence of exacerbation (patients could be recruited during exacerbations but were investigated after a stable period of at least 2 months), (3) ability to perform a six-minute walk test.

A COPD patient is considered to have acute exacerbation if there is acute deterioration in symptoms of chronic dyspnea, sputum production, or sputum purulence. Exclusion criteria were (1) coexisting acute pulmonary tuberculosis, pulmonary fibrosis, bronchiectasis, pneumothorax, or lung cancer;(2) Death during hospital stay; (3) inability to perform spirometry or being to physically ill or mentally incapacitate to participate; (4) receiving corticosteroids or immune-suppressive medications; (5) unstable coronary artery disease; (6) significant neurological disease and (7) absence of informed consent.

All together 142 patients were screened, of which 108 were eligible according to the inclusion and exclusion criteria. Of those 85 patients agreed to participate in the study (response rate 60%). The medical records and discharge cards of all included patients were manually reviewed. Demographic and clinical data were extracted. Demographic data included age, sex, marital status, highest form of education received (low level: illiterate and primary education; high level: secondary education and graduate). Participants were asked about their smoking habits and exposure to biomass fuel. Severity of depression was estimated using Hamilton Depression Rating (HAM-D), and the quality of life was estimated using disease (COPD) specific St George's Respiratory Questionnaire (SGRQ) and Generic health related quality of life (HRQoL) SF-36 Scale.

Measurement of depression

The Hamilton Depression Rating Scale (HAM-D) is a useful way of determining a patient's level of depression before, during, and after treatment. It is administered by a clinician experienced in working with psychiatric patients. Although the HAM-D form lists 21 items, the scoring is based on the first 17. It generally takes 15-20 minutes to complete the interview and scoring the results. Eight items are scored on a 5-point scale, ranging from 0= not present to 4 = severe. Nine are scored from 0-2. The score has sensitivity:86.4% and specificity: 92.2%. According to Strik *et al* (Psychosomatics 2001), scores ranges from 0 to 27 and depending upon the total score, severity of depression was classified as follows: none (0-7), mild (8-13), moderate (14-18), severe (19-22) and very severe (23-27).

Assessments of COPD

Lung function impairment

Was assessed by spirometry after inhalation of 400 µg salbutamol using a computerized spirometer (Model vitalograph 6800; SN.PN06011Vitalograph Ltd., Ireland). Measurements followed American Thoracic Society criteriafor Spiro metric standardization and procedures (Miller *et al.*, 2005).

Exercise tolerance

Six-minute walk tests (6MWTs) were performed (American Thoracic Society, 2002) using a 25 meters walk track with two attempts conducted on the same day, at least 30 minutes apart. The patient's breathlessness was scored using modified Medical Research Council (mMRC) Dyspnea scale. The mMRC Dyspnea Scale stages five categories of breathlessness: 1 shortness of breath with strenuous exercise; 2 shortness of

breath when hurrying on level on level ground; 3 needing to stop after walking 100 meters ; 4 too breathless to leave the house. Additionally, the BODE index was calculated for classification of COPD. The score comprises body mass index (BMI), post-bronchodilator FEV1% predicted, grade of dyspnea (measured by the modified Medical Research Council dyspnea scale, MMRC) and the six-minute-walking distance (Celli *et al*., 2004). The BODE index was calculated as described: for each threshold value of FEV1% predicted, distance walked in sixminutes, and score on the MMRC dyspnea scale (Mahler and Wells, 1988), the patients received points ranging from 0 (lowest value) to3 (maximal value). For body mass index, the values were 0or 1. The points for each variable were added, so that the BODE index ranged from 0 to 10 points in each patient. The post bronchodilator FEV1%predicted was used and classified according to the three stages identified by the American Thoracic Society (Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease, 1995). The best of two 6-min walk tests performed at least 30-min apart (ATS statement, 2002) was taken as asurrogate for exercise. Finally, after obtaining the BODE index for all patients, quartiles of the BODE index were used to construct four severity stages (Celli *et al*., 2004):

BODE stage 1 = BODE index 0 – 2; BODE stage 2 = BODE index 3 – 4;
BODE stage 3 = BODE index 5 – 6; BODE stage 4 = BODE index 7 – 10.

Health related quality of life *(HRQoL)*

Was measured using the disease (COPD) specific St George's Respiratory Questionnaire (SGRQ) and SF-36 Generic health related quality of life (HRQoL) Scale. Burden of symptoms, physical and social functional status and impairment of quality of life were measured using the validated Hindi version of "Saint George Respiratory Questionnaire" (SGRQ) which is a self-administered disease-specific health-related quality-of-life(HRQoL) measure, ranging from zero (indicating no impairment) to 100 (Jones *et al*., 1992). Higher scores indicate a worse health status. The questionnaire assesses the patient's experience of symptoms, the amount of distress caused by symptoms, and the daily limitation of activities. It has been well validated for use in medical patients. The SF-36 is a generic quality-of-life instrument that has two summary measures: The Physical Component Summary (PCS) and the Mental Component Summary (MCS) (Ware *et al*., 1995). Scores range from zero (worst possible impairment) to 100 (good quality of health). Most of these studies that examined the reliability of the SF-36 have exceeded 0.80 (McHorney *et al*, 1994). Estimates of reliability in the physical and mental sections are typically above 0.90. The SF-36 is also well-validated to be used for hospital patients (McHorney *et al*., 1994). The SF-36 has eight scaled scores; the scores are weighted sums of the questions in each section including vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health.

Statistical analysis

Depending on the variable distribution, results were expressed as numbers, percentages and mean ± standard error of mean. Prevalence of depression was determined by calculating the percentage of patients with the severity symptoms on HAM-D.

The association between depressive symptoms and risk determinants of severity of COPD is analyzed by performing linear regressions analysis and using age, sex and smoking status as covariates, keeping HAM-D score as dependent variable and all demographic variables (age, gender, literacy) and COPD related variables (BODE Index, SGRQ symptoms, impact and activity score, GOLD Scale, mMRC Scale, CAT Score for respiratory symptoms, SF-36 -generic quality of life) as independent variables. Difference in characteristics between participants were tested with unpaired t test for normally distributed variables, with the Wilcoxon ranksum test for skewed variables, and with the chi-square test or fisher exact test for categorical variables. Cronbach alpha was calculated to assess internal consistency of HAM-D. All statistical analyses were carried out using Statistical Package for Social Sciences (SSPS) (Version 21.0, USA).

RESULTS

Demographical, social and clinical characteristics

A total of 85 patients with COPD were included in the study. Study population included majority of men 68(80%) as compared to women 17(20%). Mean age of male and female population was 51.22±15.44 {mean ± standard deviation (SD)} years and 45.29±14.15 years respectively (Table 1). A total of 48 (56.47%) patients were either current or past smokers and 48(56.47%) were of low education (illiterate or primary school). Prevalence of smoking was more in males compared to females (Table 3). Compared to female, male patients had significantly higher proportion of illiterate patients (57.1 vs 52.9%) (Table 2). A total of 36(42.55%) patients were suffering from mild COPD, 49(57.64%) patients were suffering from moderate to very severe COPD according to GOLD consensus. There was no significant difference in severity of COPD or dyspnea level between male and female groups. The BODE Index, SGRQ Symptoms, impact and activity score, GOLD Scale, mMRC Scale, CAT Score for respiratory symptoms, SF-36 -generic quality of life was not significantly different between the two gender groups (Table I).

Prevalence of depression

Of the study population, depression was present in 51.76% (n=44). Depression score (mean HAM-D Score± SD) in moderate to very severe COPD was 12.35 ± 9.18(p=.01) (Table 4). Scores (mean ± SD) determining severity of COPD in depressed subjects were; CAT (17.45 ± 5.52), SGRQ_I (43.73% ± 15.50%), SGRQ S (59.39% ± 21.83%) and SGRQ_A (38.27% ± 20.30%). Scores (mean ± SD) determining generic quality of life in depressed subjects were SF-36 PCS (62.64% ± 11.78%) and SF-36 MCS (41.36% ± 20.86%). Except for GOLD Scale, SGRQ_I and SF-36-PCS scale, all others were statistically significant (Table 6). Depression was found to be higher among patients with severe stages of COPD with higher CAT Score, SGRQ_S Score, SGRQ_A Score and SF-36-MCS scale (HRQoL) Score. Internal consistency of HAM-D was evaluated using Cronbach alpha.

Determinants of depression

Determinants for depression in COPD patients were analyzed using linear regression model using score of HAM-D as a

dependent factor with univariate independent factors such as demographic, social and clinical factors (Table 5). Activity components of SGRQ was significantly associated with higher score of HAM-D in COPD patients (beta=.254, P=0.015). GOLD Scale (beta=.094), mMRC Scale (beta=.169), Impact component of SGRQ (beta=.254), CAT Score for respiratory symptoms (beta=.085) and SF-36 -generic quality of life: Physical (beta=.108) and Mental (beta=.186) components were not associated. Higher age, gender and smoking status were not associated with higher scores of HAM-D.

Table 1. Demographic, Clinical and Social characteristics of COPD Patients

	Sex	N	Mean	Std. Deviation	Std. Error Mean	P value
Age	Male	68	51.2206	15.44064	1.87245	.154
	Female	17	45.2941	14.15876	3.43400	
CAT	Male	68	16.7500	6.43538	.78041	.074
	Female	17	13.6471	5.88368	1.42700	
MMRC	Male	68	2.0000	.89776	.10887	1.0
	Female	17	2.0000	1.11803	.27116	
Gold	Male	68	1.8676	1.02075	.12378	.291
	Female	17	1.5882	.71229	.17276	
Bode	Male	68	3.1324	2.19840	.26660	.356
	Female	17	2.5882	2.00184	.48552	
SGRQ_I	Male	68	42.68	17.078	2.071	.832
	Female	17	41.71	15.960	3.871	
SGRQ_S	Male	68	54.41	24.056	2.917	.910
	Female	17	53.71	16.837	4.083	
SGRQ_A	Male	68	34.96	20.828	2.526	.276
	Female	17	29.00	16.206	3.930	
HAM_D	Male	68	10.1324	8.26953	1.00283	.697
	Female	17	11.0588	10.44312	2.53283	
SF36_MCS	Male	68	48.38	21.691	2.630	.410
	Female	17	43.59	19.878	4.821	
SF36_PCS	Male	68	61.53	13.714	1.663	.343

Table 2-Comparison of characteristics of smoking and education with gender of COPD Patients

Table 2.

		Sex	
		Male	Female
		Count	Count
Smoking	NonSmoker	37(54%)	16(94.1%)
	Smoker, Ex-smoker	31(45%)	1(5.9%)
Education	Low Education	39(57%)	9(52.9%)
	Higher Education	29(42%)	8(47.1%)

Table 3-Comparison of smoking and education with sex in COPD Patients

Pearson Chi-Square Tests

Table-3

		Sex
Smoking	Chi-square	9.134
	df	1
	Sig.	*.003*
Education	Chi-square	.108
	df	1
	Sig.	.743

Table 4. Comparison of depression scores with the severity of COPD according to GOLD Scale

	Gold	Number	Mean value	Std. Error Mean	**P VALUE**
HAM_D	> 2	49	12.35	1.311	**.01**
	< 2	36	7.56	1.201	

Table 5. Linear regression assessing factors associated with higher score of HAM-D

	Beta In	*Sig.*
CAT	*.085*	*.442*
MMRC	*.169*	*.133*
Gold	*.094*	*.394*
Bode	*.053*	*.631*
SGRQ_I	*.063*	*.576*
SGRQ_A	*.254*	*.015*
SF36_MCS	*-.186*	*.139*
SF36_PCS	*.108*	*.308*

Table 6- Comparison of severity of COPD by assessment of GOLD, CAT, SGRQ_I, SGRQ_S, SGRQ_A, SF-36 MCS, SF-36 PCS Score in depressed COPD Patients

	HAM_D	N	Mean	Std. Deviation	P value
Gold	>= 8	44	1.93	1.021	.239
	< 8	41	1.68	.907	
CAT	>= 8	44	17.45	5.526	**.048**
	< 8	41	14.71	7.047	
SGRQ_I	>= 8	44	43.73	15.506	.482
	< 8	41	41.15	18.131	
SGRQ_S	>= 8	44	59.39	21.283	*.031*
	< 8	41	48.78	23.157	
SGRQ_A	>= 8	44	38.27	20.304	*.031*
	< 8	41	28.93	18.821	
SF36_MCS	>= 8	44	41.36	20.864	*.006*
	< 8	41	53.93	20.055	
SF36_PCS	>= 8	44	62.64	11.787	.196
	< 8	41	58.93	14.423	

DISCUSSION

In our study, about 25(29.4%) of the patients with COPD were suffering from moderate to very severe depression and 60(70.6%) was suffering from mild or no depression, with overall cumulative prevalence of 51.76%. The depression was associated with the activity components of SGRQ, whereas no association was found with age, sex, smoking status, level of education, BODE Index, GOLD severity, mMRC Scale, impact components of SGRQ,CAT Score for respiratory symptoms and SF-36 -generic quality of life. However, the prevalence of depression was more common with severity of COPD (CAT score, SGRQ_S score, SGRQ_ A score) and HRQoL (SF-36 MCS Scale). Worldwide depression in COPD subjects varies from7%to80% (Katz *et al*., 2010; Tselebis *et al*., 2013; DiMarco *et al*., 2006). A systematic review conducted by Solano *et al* suggested that severe COPD have 37% to 71% of

clinical depression. However, instable COPD, the prevalence ranges from 10% to 42%. The cumulative prevalence of depression in cross-sectional studies of Indian COPD patients was 72% (De, 2011). In the current study, prevalence rates of depression go in accordance with the abovementioned studies and also explained by the fact that majority of individuals recruited in the study were of severe and very severe COPD. This variation in prevalence can be partly attributed to the use of different measures for depression. In agreement with the previous studies, our study also reveals that age and gender was not associated with the depression in COPD patients, it was also in accordance with the worldwide ECLIPSE study conducted by Hanania *et al* (Hanania *et al*., 2011) and postulating that depression is more related to severity of COPD than habits of smoking. Although smoking, hypoxia, and inflammation have potential impact on the prevalence of depression in COPD, the strongest predictors of depression among patients with COPD are their severity of symptoms and reported poor quality of life (Hanania *et al*., 2011; Harish Negi *et al*., 2014). Because of predominant bidi and hukkah smoking in males of northern part of India, COPD is more prevalent in males in Indian studies. Our study also goes in accordance with that of Al Shair *et al* postulating about the level of education strongly associating with the presence of depressive symptoms (Alshair *et al*., 2009).

Scarcity of Indian and worldwide data correlating the severity of the lung function impairment with the severity of anxiety and depression is a subject of research. In most studies FEV1 was a bad predictor of anxiety and depression (Ng *et al*., 2007; Dahlen and Janson, 2002; Hill *et al*., 2008). Dyspnea has been shown to correlate with anxiety and depression in patients with COPD (Mishima *et al*., 1996), on the other hand, the presence of respiratory symptoms cause substantial depression in COPD patients (Janson *et al*., 1994). Another important variable, which showed strong association with COPD was BODE Index. However, BODE index is closely related to the individual's subjective consequences of COPD severity and its complications rather than lung functional one. Symptoms of depression in COPD are associated with poorer HRQoLinCOPD. The long itudinal impact of depression and anxiety on HRQoL was conducted by Blake more *et al* suggesting that both depression and anxiety at base line are significantly associated with worsening levels of HRQoL (Balcells *et al*., 2010; Tsiligianni *et al*., 2010; Blakemore *et al*., 2014). Our findings were in accordance with the previous studies that dyspnea (activity component of SGRQ) is most important predictor associated with the development of depressive symptoms. Psychiatric comorbidities encountered in our patients was mainly due to dyspnea leading to physical impairment. Hence, the factors involved with depression are postulated to be more linked to reduced functional activity of COPD patients rather than gender or other disease specific factors.

There were certain limitations in our study.We were not able to recruit a large sample size and study population was not randomly assigned for our study population. Also, we did not include any physical activity questionnaires to know overall impairment in physical activity, which will be our future target of research. Additionally, the strengths of our study involve the incorporation of questionnaires measuring the overall functional status by SGRQ Scale, mMRC scale, GOLD Scale, BODE Index and SF-36 HRQoL Scalein it. Therefore, the relationship of functional status with health-related quality of life and psychological health outcomes was appropriately measured. Future studies should be targeted with large sample size and longitudinal impact of behavioral and rehabilitation therapies over the depression and quality of life. Future studies should be conducted to identify the outcomes of COPD with early screening and appropriate treatment for depression.In addition, guidelines regarding the minimum duration of cognitive behavioral therapies is lacking in Indian data source. Therefore, routine clinical practice should inculcate early identification and treatment of psychological comorbiditiesin COPD patients.

Conclusion

A substantial number of patients with COPD had depression with higher occurrence of depression among with higher dyspnea and COPD severity, and with poor quality of life. There is need for appropriate screening tool and mental health counselors to be provided along with general physicians at the primary health care levels in rural India before depression becomes endemic.

Acknowledgment

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethics approval and consent to participate: Written informed consent was obtained from the patient. The case report was approved by the Institutional Ethics Committee.

Abbreviations: COPD (chronic obstructive pulmonary disease); GOLD (The Global Initiative for Chronic Obstructive Lung Disease); FEV1 (forced expiratory volume in one second); HAM-D (Hamilton depression Scale); CAT (COPD Assessment Test), SGRQ (St George's Respiratory Questionnaire); SF-36 (SHORT FORM-36); HRQoL(Health Related Quality of Life); mMRC(modified Medical Research Council dyspnea scale); BODE (BMI, Obstruction, Dyspnea, Exercise Capacity).

REFERENCES

Alshair K, Dockry R, MalliaMilanes B, Kolsum U, Singh D, Vestbo J. 2009. Depression and its relationship with poor exercise capacity, BODE index and muscle wasting in COPD. *Respir Med*., 103:1572–9.

American Thoracic Society. ATS statement: guidelines for thesix-minute walk test. *Am J Respir Crit Care Med*., 2002; 166:111–7.

ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*., 2002, 166:111-117.

Ayuso-Mateos JL, Vazquez-BarqueroJL, Dowrick C, *et al*. 2001. Depressive disordersin Europe: prevalence figures from the ODINstudy. *BrJ Psychiatry*, 179:308–316.

Balcells E, Gea J, Ferrer J, *et al*. 2010. Factors affecting the relationship between psychological status and quality of life in COPD patients. *Health Qual Life outcomes*, 8:108.

Barnes PJ. and Celli BR. 2009. Systemic manifestations and comorbidities of COPD. *Eur Respir J*., 33(5):1165–1185.

Blakemore A, Dickens C, Guthrie E, *et al.* 2014. Depressionandanxiety predict health-related quality of life in chronic obstructive pulmonary disease: systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.*, 9:501–512.

Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. 2004. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. *N Engl J Med.*, 350:1005-1012.

Cully JA, Graham DP, Stanley MA, *et al.* 2006. Quality of life inpatients with chronic obstructive pulmonary disease and comorbid anxiety or depression. *Psychosomatics*, 47:312–319.

Dahlen I. and Janson C. 2002. Anxiety and depression are related to theoutcome of emergency treatment in patients with obstructivepulmonary disease. *Chest,* 122:1633-1637.

Dalal AA, Shah M, Lunacsek O, *et al.* 2011. Clinical and economic burden of depression/anxiety in chronic obstructive pulmonary disease patients within a managed care population. COPD, 8: 293–299.

De S. 2011. Prevalence of depression in stable chronic obstructive pulmonary disease. *Indian Journal of Chest Diseases and Allied Sciences*, 53(1): 35.

DiMarco F, Verga M, Reggente M, *et al.* 2006. Anxiety and depression in COPD patients:the roles of gender and disease severity.*RespirMed.*, 100:1767–1774.

Domingo-Salvany A, Lamarca R, Ferrer M. *et al.* 2002. Health related quality of life and mortality in male patients with chronicob structive pulmonary disease. *Am.J.Respir.Crit. CareMed.*,166:680–5.

Dowson CA, Town GI, Framptom C, *et al.* 2004. Psychopathology and illness beliefs influence COPD self-management. *JPsychosomRes.*, 56(3):333–340.

Ferrari AJ, Charlson FJ, Norman RE, *et al.* 2013. Burden of depressive dis-orders by country, sex, age, andyear: findings from the Global Burden of Disease Study, 2010. *PLoS Med.*, 10(11):e1001547.

Global Initiative for Chronic Obstructive Lung Disease.Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.2016. Available from: http://www.goldcopd.org, accessed April, 2017.

Hanania NA, Mullerova H, Locantore NW, *et al.* 2011. Determinants of depression in the ECLIPSE chronic obstructive pulmonary disease cohort. *Am J Respir Crit Care Med.*, 183:604–611.

Harish Negi, Malay Sarkar *et al.* 2014. Presence of depression & its risk factors in patients with chronic obstructive pulmonary disease. *Indian J Med Res.*, 139, March,pp 402-408.

Hill K, Geist R, Goldstein RS, Lacasse Y. 2008. Anxiety and depressionin end-stage COPD. *Eur Respir J.*, 31:667-677.

Janson C, Bjornsson E, Hetta J, Boman G. 1994. Anxiety and depressionin relation to respiratory symptoms and asthma. *Am J Respir Crit Care Med.*, 149:930-934.

Johnson G, Kong DC, Thoman R. 2005. Factors associated with medication on adherence in patients with COPD. *Chest*, 128(5):3198–3204.

Jones PW, Quirk FH, Baveystock CM, Littlejohns P. 1992. A self-complete measure of health status for chronic airflow limitation. The St.George's Respiratory Questionnaire. *Am Rev Respir Dis.,* 145: 1321-1327.

Katz PP, Julian LJ, Omachi TA *et al. 2010.* The impact of disability on depression among individuals with COPD. *Chest,* 137, 838–845.

Kosmas E, Tselebis A, Bratis D, *et al.* 2014. The Relationship between the adherence to treatment and the psychological profile of patients with chronic obstructive pulmonary disease. *Chest*, 145(3_MeetingAbstracts):377A.

Kunik ME, Roundy K, Veazey C, *et al*. 2005. Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. *Chest*, 127:1205–1211

Lacasse Y, Rousseau L, Maltais F. 2001. Prevalence of depressive symptoms and depression inpatients with severe oxygen-dependent chronic obstructive pulmonary disease. *JCar- diopulm Rehabil.*, 21:80–86.

Mahler DA. and Wells CK. 1988. Evaluation of clinical methods for rating dyspnea.*Chest*, 93:580-586.

Mannino DM, Kiriz VA. 2006. Changing the burden of COPD mortality. *IntJ Chron Obstruct Pulmon Dis.*, 1(3):219–233.

McHorney CA, Ware JE, Lu JFR, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36®): III. tests of data quality, scaling assumptions and reliabilityacross diverse patient groups. *MedCare,* 1994; 32(4):40-66.

Miller MR, Hankinson J, Brusasco V *et al.* 2005. Standardisation of spirometry. *Eur Respir J.*, 26:319-338

Mishima M, Oku Y, Muro S, Hirai T *et al.* 1996. Relationship between dyspnea in daily life and psycho-physiologic state in patients with chronic obstructive pulmonary disease during long-term domiciliary oxygen therapy. *Intern Med.,* 35:453-458.

Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. 2007. Depressive symptoms and chronicob structive pulmonary disease:effectonmortality, hospital readmission, symptom burden, functional status, and quality of life. *Arch Intern Med.*, 167(1):60–67.

Oga T, Nishimura K, Tsukino M, *et al.* 2003. Analysis of the factors related to mortality in chronicob structive pulmonary disease. Role ofexercise capacity and health status. *Am.J.Respir.Crit. CareMed.*, 167:544–9.

Ozkaya S, Findik S, Atici AG. 2011. The cost of hospitalization in patients with acute exacerbation of chronic obstructive pulmonary disease. *Clinicoecon Outcomes Res.*, 3:15–18.

Skultety KM. and Zeiss A. 2006. The treatment of depression in older adultsin the primary care setting: an evidence-based review. *Health Psychol.*, 25: 665-74.

Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease.American Thoracic Society. *Am J Respir Crit Care Med.,* 1995, 152:S77-121.

Tselebis A, Bratis D, Pachi A, *et al*. Anxiety and depression inpatients with chronicob structive pulmonary disease (COPD). In:ZirimisL, Papazoglakis A, editors.*Chronic Obstructive Pulmonary Disease: NewResearch*. NewYork, NY:NovaSciencePublishers; 2013:15–40. ISBN:978-1-62081-848.

TsiligianniI G, vanderMolen T. 2010. A systematic review of the role of vitaminin sufficiencies and supplementation in COPD. *RespirRes.*, 11:171.

van Manen JG, Bindels PJ, Dekker FW, et al. 2002. Risk of depression in patients with chronic obstructive pulmonary disease and its determinants. *Thorax*, 57:412–416.

Ware JEJ, Kosinski M, Bayliss MS, McHorney CA, Rogers WH Raczek A. Comparison of methods for the scoring and statistical analysis of SF 36 health profile and summary

measures: summary of results from the Medical Outcomes Study. Med Care 1995; 33(Suppl. 4): AS264–79.

Xu W, Collet JP, Shapiro S, *et al. 2008.* Independent effect of depression and anxiety on chronic obstructive pulmonary disease exacerbations and hospitalizations. *Am. J. Respir. Crit. CareMed.,* 178, 913–920.

Yohannes AM, Baldwin RC, Connolly MJ. 2006. Depression and anxiety in elderly patients with chronic obstructive pulmonary disease. *Age Ageing.*, 35(5):457–459.

Yohannes AM. 2008. Management of anxiety anddepression in patients with COPD. *ExpertRev. Resp. Med.,* 2, 337–347.

****