

Original Research

Clinical Characteristics of Patients With COPD and Comorbid Depression and Anxiety: Data From a National Multicenter Cohort Study

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Abbreviations: MINI: Mini International Neuropsychiatric Interview; CAT: COPD Assessment Test; COPD: Chronic obstructive pulmonary disease; U.S.: United States; HADS: Hospital Anxiety and Depression Scale; PHQ-9: Patient Health Questionnaire-9; ACE: Anxiety and COPD Evaluation; ALA-ACRC: American Lung Association Airways Clinical Research Center; FEV₁: Forced expiratory volume in one second; FVC: Forced vital capacity; MoCA: Montreal

Cognitive Assessment; PSQI: Pittsburgh Sleep Quality Index; EQ-5D-5L: Euro Quality of Life; GAD-7: Generalized Anxiety Disorder-7; PROMIS-29: Patient-Reported Outcomes Measurement Information System-Anxiety and Physical Function

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Abstract

Background

Most studies on mental health among individuals with COPD utilize screening questionnaires, which detect psychiatric *symptoms*, but cannot be used to *diagnose* depression/anxiety disorders. We utilized the Mini International Neuropsychiatric Interview (MINI) to identify depression/anxiety disorders meeting DSM-V diagnostic criteria and described associated disease burden in people with COPD.

Methods

This is a cross-sectional, secondary analysis of a multi-center study designed to evaluate anxiety questionnaires in COPD patients. Research coordinators administered both the MINI and screening questionnaires to determine participants who met diagnostic criteria for depression/anxiety disorders and capture symptom burden, respectively. Bivariate analyses were conducted to assess differences in COPD and patient-reported outcomes between those with and without depression/anxiety disorders.

Results

Of 220 participants, 18 (8%) met MINI criteria for depression and 17 (8%) for anxiety. Depression was associated with more breathlessness (Modified Medical Research Council Dyspnea Scale 4 vs 3, $p = 0.045$), higher COPD disease burden (COPD Assessment Test (CAT) 27 vs. 17, $p < 0.001$), worse sleep quality (Pittsburgh Sleep Quality Index 11 vs. 7, $p = 0.001$) and health-related quality of life (Euro Quality of Life 0.31 vs. 0.59, $p < 0.001$). Anxiety was associated with lower CAT scores, and worse health-related quality of life and function. Most with depression/anxiety disorders were not using anti-depressants/anxiolytics, or receiving mental health counseling.

Conclusion

Depression and anxiety disorders meeting diagnostic criteria are relatively common comorbidities that substantially impair quality of life and are undertreated, highlighting a need to prioritize mental health as an integral part of comprehensive COPD care.

Pre-proof

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) affects over 15 million adults in the United States (U.S.) and has a substantial impact on quality of life, representing the second most common cause of disability-adjusted life years lost in the U.S.^{1,2} Psychiatric symptoms are common among individuals with COPD, with 15-56% and 16-55% reporting depressive and anxiety symptoms, which carry important implications for COPD outcomes and disease trajectory.³⁻⁶ Depressive symptoms have been associated with premature mortality, increased length of hospital stay and reduced functional capacity, as well as greater breathlessness and lower adherence to COPD treatments.⁷⁻⁹ Anxiety symptoms have been linked with increased healthcare utilization, heightened respiratory symptoms, diminished quality of life and greater mortality among people with COPD.¹⁰⁻¹³

However, the vast majority of these studies utilized screening questionnaires, such as the Hospital Anxiety and Depression Scale (HADS)¹⁴ and Patient Health Questionnaire-9 (PHQ-9),¹⁵ which are commonly used to identify depressive and anxiety *symptoms*, but cannot be used to establish a *diagnosis*. Although psychiatric symptoms and diagnoses exist on a continuum, there may be differences between people with COPD and heightened psychiatric symptoms and those meeting diagnostic criteria for depression or an anxiety disorder. Despite existing literature on a clear relationship between COPD and both depressive and anxiety symptoms based on screening questionnaires, there is a paucity of data using well-validated diagnostic instruments such as the Mini-International Neuropsychiatric Interview (MINI). The MINI is a structured interview used as a gold standard for identifying depression and anxiety disorders based on DSM-V diagnostic criteria in situations where interview with a psychiatrist is not feasible.^{16,17} One national multi-center observational survey study (Anxiety and COPD Evaluation (ACE)

evaluated anxiety screening questionnaire performances among COPD patients using the MINI as the gold standard assessment for the diagnosis of anxiety disorders.¹⁸ This study observed that screening questionnaires for anxiety symptoms in COPD patients had only fair to moderate psychometric screening properties. In this study, we performed a secondary analysis of the ACE study, using the MINI to identify individuals meeting diagnostic criteria for depression and anxiety disorders and report clinical characteristics and disease burden of these comorbidities among individuals with COPD.

METHODS

Study design and participants

This is a cross-sectional, secondary analysis of a multi-center study in stable patients with COPD enrolled at 16 centers within the American Lung Association Airways Clinical Research Center (ALA-ACRC) network in the U.S. Other data have been previously reported from this cohort.^{18,19} Briefly, enrolled participants were ≥ 40 years of age, had a confirmed diagnosis of COPD (defined by a forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio of less than 0.7 and a post-bronchodilator $FEV_1 < 80\%$ predicted),¹ and considered to have clinically stable COPD (absence of exacerbation or worsening symptoms requiring antibiotic or corticosteroids in the 6 weeks prior to enrollment). Those with unstable coronary heart disease, untreated cardiac arrhythmia, unstable angina, major uncontrolled psychiatric disorders that would affect study participation, significant cognitive impairment (defined by Montreal Cognitive Assessment (MoCA) < 18),²⁰ or a condition expected to cause death or inability to perform study procedures within 6 months were excluded. COPD severity was assessed using GOLD criteria for grading airflow obstruction and categorized as GOLD 2 (FEV_1

≥50% and <80% predicted), GOLD 3 (FEV₁≥30% and <50% predicted) or GOLD 4 (FEV₁<30% predicted).¹ Written consent was obtained from all participants and the study was approved by institutional review boards for clinical centers and the data coordinating center.

Procedures and instruments

Enrolled participants provided demographic and clinical characteristics and underwent a physical examination, spirometry testing and six-minute walk test. Trained research coordinators administered questionnaires on patient-reported symptoms, followed by the structured MINI version 7.0 diagnostic interview. Questionnaires included the Modified Medical Research Council Dyspnea Scale (MMRC),²¹ COPD Assessment Test (CAT),^{22,23} Pittsburgh Sleep Quality Index (PSQI),²⁴ Euro Quality of Life (EQ-5D-5L),^{25,26} Generalized Anxiety Disorder-7 (GAD-7),²⁷ HADS,¹⁴ PHQ-9,¹⁵ and Patient-Reported Outcomes Measurement Information System-Anxiety and Physical Function (PROMIS-29).²⁸ Cognitive impairment was assessed using the MoCA test, with a score of 18-25 considered to be mild cognitive impairment.²⁰ The MINI was used as the gold standard for the identification of major depressive and/or anxiety disorders based on DSM-V diagnostic criteria.^{16,17} Specifically, sections on major depressive and anxiety disorders (panic disorder, social anxiety disorder, generalized anxiety disorder, post-traumatic stress disorder, agoraphobia) were administered. Questions elicited a “yes/no” response, and a point was given for each “yes” response. Although the primary analysis of this study evaluating questionnaire performance included lifetime history of panic disorder under anxiety disorders,¹⁸ this current analysis classified individuals as having a mood or anxiety disorder based on current symptoms rather than lifetime history. Licensed clinical psychologists reviewed audio recorded interviews conducted by coordinators for quality assurance and certification.

Statistical analysis

This is a secondary analysis of data collected from a completed cohort study evaluating the sensitivity and specificity of anxiety questionnaires.¹⁸ For this analysis, we summarized socioeconomic and clinical characteristics and patient-reported outcomes, stratified by the presence of current depression and/or anxiety disorder based on MINI interviews at enrollment. We calculated medians and quartiles for the continuous variables and frequencies and proportions for categorical variables. Differences between strata were evaluated using Kruskal-Wallis and Chi-square tests or Fisher's exact tests for continuous and categorical variables, respectively. Bivariate analyses were conducted to determine differences in patient-reported outcomes based on validated questionnaires between those with and without depression or an anxiety disorder. A p-value less than 0.05 was considered statistically significant. Because of the small number of cases, multivariate analyses were not performed. All analyses were post hoc (not planned in the study protocol). Data were analyzed using SAS version 9.4 (SAS Institute).

RESULTS

Of 282 individuals screened, 220 eligible participants were enrolled in the study between May 2016 and December 2016. Among the excluded individuals, 45 did not meet spirometric criteria for at least moderate severity COPD, 12 had a MoCA score ≤ 18 , and 5 were not eligible based on both those criteria.

Major Depressive Disorder

Among the total cohort, 18 (8%) participants met MINI diagnostic criteria for current major depressive disorder. In contrast, 103 (46.8%) participants screened positive for at least mild depressive symptoms with scores ≥ 5 on the PHQ-9 questionnaire. Participants with major depressive disorder were younger (median age 60 vs. 66 years, $p = 0.016$) and a greater proportion had a household income $< \$22,000$ (61% vs. 30%, $p = 0.014$), compared to those without depression (Table 1). There were no significant differences in COPD severity by GOLD classification, spirometric lung function, use of supplemental oxygen, 6-minute walk distance, inhaler use or recent history of acute COPD exacerbations between those with and without depression.

Current depression meeting MINI diagnostic criteria was associated with worse patient-reported outcomes, including greater breathlessness (MMRC 4 vs 3, $p = 0.045$) and COPD-associated symptom burden (CAT 27 vs. 17, $p < 0.001$), as well as worse sleep quality (PSQI 11 vs. 7, $p = 0.001$), and impaired quality of life (EQ-5D 0.31 vs. 0.59, $p < 0.001$; PROMIS-29 physical function 34 vs. 39, $p = 0.002$) (Table 2). Participants with depression also reported worse depressive and anxiety symptoms on standard screening questionnaires. Median MoCA scores were 25, which is indicative of mild cognitive impairment, in both those with and without depression (Table 2).

Among participants with major depressive disorder, only 7 (39%) reported using antidepressant medications and 4 (22%) were receiving mental health counseling. These participants were also more likely to have a concurrent anxiety disorder meeting MINI diagnostic criteria (28% vs. 6%, $p = 0.004$) (Table 1).

Anxiety Disorders

In this cohort, 17 (8%) participants met MINI diagnostic criteria for a current anxiety disorder (Table 1). Agoraphobia was the most common, affecting 10 (59%) participants with current anxiety (Table 3). In contrast, a greater number of people screened positive for at least mild anxiety symptoms, with 38 (17%) reporting a HADS Anxiety score ≥ 8 , and 65 (30%) reporting a GAD-7 score of >4 . Patients who met and did not meet MINI diagnostic criteria for a current anxiety disorder had similar demographic characteristics, although those with anxiety were younger at enrollment (59 vs. 65 years, $p = 0.018$). Like participants with depression, those with an anxiety disorder experienced more depressive and anxiety symptoms, had generally worse scores on patient-reported measures of disease-specific symptom burden and health-related quality of life, and on most of the PROMIS-29 metrics of well-being (Table 2). However, fewer than half of participants with a current anxiety disorder used anxiolytics or anti-depression medications or received mental health counseling (Table 1).

Based on MINI interviews, only 5 (2%) participants had a concomitant diagnosis of depression and anxiety (Table 1). Three of these 5 were male and reported greater symptom burden, and three ranked in the lowest quartile for the 6-minute walk distance and had lower than median lung function. Four had mild cognitive impairment.

DISCUSSION

This is the first multi-center study to describe the sociodemographic and clinical characteristics of individuals with COPD and major depressive and/or anxiety disorders meeting MINI diagnostic interview criteria based on the DSM-V. Data were collected in a study conducted at 16 ALA-ACRC centers with the primary aim of determining the sensitivity and specificity of questionnaire measures of anxiety in people with COPD. In this secondary

analysis, we found that participants with diagnosed depression or anxiety disorders experienced greater COPD-associated respiratory symptom burden, reduced functionality and health-related quality of life, compared to those without either psychiatric disorder. Notably, both depression and anxiety were undertreated in this cohort, with substantially fewer than half using an anxiolytic or anti-depressant, or undergoing mental health counseling. Despite a growing awareness of psychiatric comorbidities among patients with COPD over the past decade, there remains limited national consensus and clinical guidelines on practical approaches to screening for and managing comorbid mood and anxiety disorders.⁴ Thus, this study highlights a persistent, major gap in mental health care among patients with COPD.

We also observed that screening questionnaires, including the PHQ-9, HADS Anxiety and GAD-7, detected more individuals with depressive and anxiety symptoms (47% and 17-30%, respectively) than those who met MINI diagnostic criteria for having a major depressive or anxiety disorder (8% each). Unlike screening instruments – which are inherently designed to have higher sensitivity and lower specificity to reduce the probability of missing a diagnosis – the well-validated MINI is designed to identify major depressive and anxiety disorders based on DSM-V diagnostic criteria. Furthermore, commonly used screening questionnaires cannot accurately distinguish psychiatric from somatic symptoms that may coexist among COPD patients and lack detailed measures of functional impairment required to meet diagnostic criteria.^{3,18} As a result, findings from this study using the MINI diagnostic assessment extends existing knowledge on relationships between depressive and anxiety *symptoms* and patient-reported outcomes to also include those meeting MINI *diagnostic criteria* for depression and anxiety disorders.

Participants with major depressive disorder meeting MINI diagnostic criteria were significantly younger, and a greater percentage reported lower household income compared to those without depression. Individuals with anxiety disorders meeting MINI diagnostic criteria were also significantly younger than those without anxiety. The few participants with concurrent depression and anxiety had more severe COPD and greater symptom burden. Otherwise, there were no significant differences in demographic or clinical characteristics among those with and without depression or anxiety disorders.

However, compared to those without either psychiatric disorder, patients with depression or anxiety disorders experienced more functional impairment and disability due to COPD-associated respiratory symptoms, poorer quality of sleep, and reduced health-related quality of life, including increased fatigue and pain limiting daily activities. This is consistent with and extends prior work using screening questionnaires that linked elevated depressive and anxiety *symptoms* with reduced COPD-associated quality of life.^{6,29} These findings are important, as uncontrolled psychiatric comorbidities may contribute to maladaptive behaviors that influence COPD disease trajectory and perpetuate a cycle of disabling symptoms.^{3,30} For example, poorly controlled depression and anxiety disorders may reduce disease-related coping, impair self-care behaviors such as participation in pulmonary rehabilitation and adherence to smoking cessation, and promote poor medication adherence, all of which increases risk for COPD exacerbations and hospitalizations.^{6,10,31-35} In this regard, we have found that the most common anxiety comorbidity in this cohort is agoraphobia, a condition which can limit activity, healthcare use, and social involvement.³⁶ Anxious feelings of fear and worry may also amplify symptoms typically attributed to COPD, including heightened sensations of breathlessness and poor exercise tolerance. These experiences then lead to further social isolation, sensations of panic, and

feelings of helplessness, perpetuating a cycle of reciprocal symptoms.^{33,37-39} This bidirectional, intertwined relationship between psychiatric disorders and COPD further highlights the gravity of mental health as an integral but underappreciated component of COPD care.^{40,41}

Despite this, there remains a lack of widespread clinical awareness of these psychiatric disorders resulting in under recognition and undertreatment.^{3,41} One prior cross-sectional study from nearly two decades ago identified that fewer than a third of COPD patients with depression or anxiety were receiving psychiatric treatment.⁴² Our study affirms a persistent care gap, with only a minority of participants with depression or anxiety in this cohort who reported using anxiolytics and/or antidepressants, or receiving mental health counseling. Furthermore, those with diagnosed depression or anxiety scored poorly on metrics evaluating health-related quality of life and reported a high burden of depressive or anxiety symptoms, suggesting inadequate treatment. These results emphasize a necessity for not only timely recognition and diagnosis, but also an integrated multi-disciplinary support network for the effective treatment of these common mental health comorbidities in patients with COPD.

This study has notable strengths. Our cohort included participants from multiple centers across the United States, enhancing generalizability. We utilized both the structured MINI with trained administrators to accurately identify those meeting diagnostic criteria for depression or anxiety disorders and administered several screening questionnaires to concurrently gauge depressive and anxiety symptom burden and functional impact. While the MINI has been used in COPD patients in smaller single-center studies,^{43,44} ours is the first and largest multi-center study to describe characteristics between individuals who meet MINI diagnostic criteria for depression and anxiety disorders and those who do not. However, we also acknowledge several limitations. The main aim of this study was to describe clinical characteristics of COPD patients with

depression and anxiety disorders and to capture the burden of these psychiatric disorders in this population. However, the relatively low number of participants with depression or anxiety disorders based on MINI diagnostic criteria potentially reduced power to account for confounders and evaluate associations and inter-dependencies between COPD characteristics and depression or anxiety disorders. Furthermore, as this was a cross-sectional analysis, it remains unclear how symptoms may change over time throughout the disease course, and if alleviating the burden of psychiatric disorders would improve COPD outcomes. However, our study serves to inform larger, longitudinal studies dedicated to understanding how mental health comorbidities may influence both patient-reported outcomes and COPD disease trajectory.

CONCLUSIONS

This cross-sectional analysis of a national, multi-center cohort of patients with COPD found that major depressive and anxiety disorders meeting MINI diagnostic interview criteria based on the DSM-V were relatively common comorbidities that remain underrecognized and undertreated, despite a profound impact on symptom burden affecting daily function and quality of life. There is a need to understand patient and systems-level barriers to the accurate diagnosis of mood and anxiety disorders in this population, and for effective strategies to manage these conditions as an integral part of comprehensive COPD care.

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DECLARATION OF GENERATIVE AI IN SCIENTIFIC WRITING

We declare that no part of this manuscript was written with the use of artificial intelligence.

AUTHOR CONTRIBUTIONS

JGW, SB, LN and JTH contributed to data analyses and interpretation and manuscript writing. NAH, AMY, MNE and RAW contributed to the conception of the study, and data collection, analyses and interpretation. All authors revised the manuscript for intellectual content and approved the final version of the manuscript.

Declarations of interests:

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NAH discloses that he received honoraria for serving as an advisor/consultant for GSK, Sanofi, Genentech, Verona Pharma, Astra Zeneca and Boehringer Ingelheim, and research support from GSK, Sanofi, Astra Zeneca and Genentech.

JGW, JTH, LN, AMY and RAW do not have any declarations of interest.

*A complete list of members for the American Lung Association Airway Clinical Research Centers may be found below.

Pre-proof

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REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. 2023 GOLD Report. <https://goldcopd.org/2023-gold-report-2/>, January 25, 2023.
2. Wheaton AG, Cunningham TJ, Ford ES, Croft JB. Employment and activity limitations among adults with chronic obstructive pulmonary disease--United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2015;64(11):289-295.
3. Yohannes AM, Alexopoulos GS. Depression and anxiety in patients with COPD. *European Respiratory Review*. 2014;23(133):345-349.
4. Matte DL, Pizzichini MM, Hoepers AT, et al. Prevalence of depression in COPD: A systematic review and meta-analysis of controlled studies. *Respir Med*. 2016;117:154-161.
5. Hanania NA, Müllerova H, Locantore NW, et al. Determinants of Depression in the ECLIPSE Chronic Obstructive Pulmonary Disease Cohort. *American Journal of Respiratory and Critical Care Medicine*. 2011;183(5):604-611.
6. Yohannes AM, Willgoss TG, Baldwin RC, Connolly MJ. Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. *Int J Geriatr Psychiatry*. 2010;25(12):1209-1221.
7. Volpato E, Toniolo S, Pagnini F, Banfi P. The Relationship Between Anxiety, Depression and Treatment Adherence in Chronic Obstructive Pulmonary Disease: A Systematic Review. *Int J Chron Obstruct Pulmon Dis*. 2021;16:2001-2021.
8. Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. *Arch Intern Med*. 2007;167(1):60-67.
9. Hilmarsen CW, Wilke S, Engan H, et al. Impact of symptoms of anxiety and depression on COPD Assessment Test scores. *European Respiratory Journal*. 2014;43(3):898-900.
10. Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;186(2):155-161.
11. Gudmundsson G, Gislason T, Janson C, et al. Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression. *European Respiratory Journal*. 2005;26(3):414-419.
12. Vikjord SAA, Brumpton BM, Mai X-M, Vanfleteren L, Langhammer A. The association of anxiety and depression with mortality in a COPD cohort. The HUNT study, Norway. *Respiratory Medicine*. 2020;171.
13. Doyle T, Palmer S, Johnson J, et al. Association of anxiety and depression with pulmonary-specific symptoms in chronic obstructive pulmonary disease. *Int J Psychiatry Med*. 2013;45(2):189-202.
14. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370.
15. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *Jama*. 1999;282(18):1737-1744.
16. Sheehan D. MINI-Mini International neuropsychiatric interview-english version 5.0. 0-DSM-IV. *J Clin Psychiatry*. 1998;59:34-57.

17. Sheehan DV, Lecrubier Y, Harnett Sheehan K, et al. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *European Psychiatry*. 1997;12(5):232-241.
18. Baker AM, Holbrook JT, Yohannes AM, et al. Test Performance Characteristics of the AIR, GAD-7, and HADS-Anxiety Screening Questionnaires for Anxiety in Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc*. 2018;15(8):926-934.
19. Yohannes AM, M NE, Holbrook JT, et al. Association of mild cognitive impairment and characteristic of COPD and overall health status in a cohort study. *Expert Rev Respir Med*. 2021;15(1):153-159.
20. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699.
21. Fletcher C. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). *Bmj*. 1960;2:1665.
22. Jones P, Harding G, Wiklund I, Berry P, Leidy N. Improving the process and outcome of care in COPD: development of a standardised assessment tool. *Primary Care Respiratory Journal*. 2009;18(3):208-215.
23. Jones PW, Harding G, Berry P, Wiklund I, Chen W-H, Kline Leidy N. Development and first validation of the COPD Assessment Test. *European Respiratory Journal*. 2009;34(3):648-654.
24. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213.
25. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727-1736.
26. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
27. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. *Archives of Internal Medicine*. 2006;166(10):1092-1097.
28. Hays RD, Spritzer KL, Schalet BD, Cella D. PROMIS®-29 v2.0 profile physical and mental health summary scores. *Quality of Life Research*. 2018;27(7):1885-1891.
29. Omachi TA, Katz PP, Yelin EH, et al. Depression and Health-Related Quality of Life in Chronic Obstructive Pulmonary Disease. *The American Journal of Medicine*. 2009;122(8):778.e779-778.e715.
30. Sundh J, Ekström M. Persistent disabling breathlessness in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2805-2812.
31. Albrecht JS, Park Y, Hur P, et al. Adherence to Maintenance Medications among Older Adults with Chronic Obstructive Pulmonary Disease. The Role of Depression. *Ann Am Thorac Soc*. 2016;13(9):1497-1504.
32. Laurin C, Moullec G, Bacon SL, Lavoie KL. Impact of anxiety and depression on chronic obstructive pulmonary disease exacerbation risk. *Am J Respir Crit Care Med*. 2012;185(9):918-923.
33. Burgess A, Kunik ME, Stanley MA. Chronic obstructive pulmonary disease: assessing and treating psychological issues in patients with COPD. *Geriatrics*. 2005;60(12):18-21.

34. Martínez-Gestoso S, García-Sanz M-T, Carreira J-M, et al. Impact of anxiety and depression on the prognosis of copd exacerbations. *BMC Pulmonary Medicine*. 2022;22(1):169.
35. Fan VS, Curtis JR, Tu SP, McDonell MB, Fihn SD. Using quality of life to predict hospitalization and mortality in patients with obstructive lung diseases. *Chest*. 2002;122(2):429-436.
36. Wittchen H-U, Gloster AT, Beesdo-Baum K, Fava GA, Craske MG. Agoraphobia: a review of the diagnostic classificatory position and criteria. *Depression and Anxiety*. 2010;27(2):113-133.
37. Han MK, Martinez CH, Au DH, et al. Meeting the challenge of COPD care delivery in the USA: a multiprovider perspective. *Lancet Respir Med*. 2016;4(6):473-526.
38. Yohannes AM, Müllerová H, Hanania NA, et al. Long-term Course of Depression Trajectories in Patients With COPD: A 3-Year Follow-up Analysis of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Cohort. *Chest*. 2016;149(4):916-926.
39. Bailey PH. The dyspnea-anxiety-dyspnea cycle--COPD patients' stories of breathlessness: "It's scary /when you can't breathe". *Qual Health Res*. 2004;14(6):760-778.
40. Atlantis E, Fahey P, Cochrane B, Smith S. Bidirectional Associations Between Clinically Relevant Depression or Anxiety and COPD: A Systematic Review and Meta-analysis. *Chest*. 2013;144(3):766-777.
41. Hill K, Geist R, Goldstein RS, Lacasse Y. Anxiety and depression in end-stage COPD. *European Respiratory Journal*. 2008;31(3):667-677.
42. Kunik ME, Roundy K, Veazey C, et al. Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. *Chest*. 2005;127(4):1205-1211.
43. Orlandi Lde C, Pinho JF, Murad MG, Rocha FL, Rodrigues-Machado MG. Depression diagnosed by the mini international neuropsychiatric interview plus (MINI) in patients with chronic obstructive pulmonary disease: relationship with functional capacity and quality of life. *BMC Res Notes*. 2016;9:65.
44. Yohannes AM, Willgoss TG. The accuracy of the anxiety inventory respiratory disease scale for patients with chronic obstructive pulmonary disease. *Int J Geriatr Psychiatry*. 2015;30(1):106-108.

Table 1. Demographic and clinical characteristics

	Overall	Current depression*		p-value	Current anxiety*		p-value
	n = 220	No (n = 202)	Yes (n = 18)		No (n = 203)	Yes (n = 17)	
Demographics							
Age, years, median (IQR)	65 (59, 72)	66 (59, 73)	60 (55, 63)	0.016	65 (59, 73)	59 (52, 67)	0.018
Male, n (%)	118 (54)	108 (54)	10 (56)	>0.999	110 (54)	8 (47)	0.754
White, n (%)	173 (79)	160 (79)	13 (72)	0.694	157 (77)	16 (94)	0.189
Household income, n (%)							
< \$22,000	72 (33)	61 (30)	11 (61)	0.014	65 (32)	7 (41)	0.222
\$22,000- \$43,999	47 (21)	42 (21)	5 (28)		41 (20)	6 (35)	
>\$44,000	68 (31)	66 (33)	2 (11)		66 (33)	2 (12)	
Don't know/refused to answer	33 (15)	33 (16)	0 (0)		31 (15)	2 (12)	
Education, n (%)							
High school degree or less	83 (38)	77 (38)	6 (33)	0.882	80 (39)	3 (18)	0.204
Some college/associate/technical	86 (39)	78 (39)	8 (45)		77 (38)	9 (53)	
Graduate or post-graduate	51 (23)	47 (23)	4 (22)		46 (23)	5 (29)	
Current or former smoker, n (%)							
Pack-years, median (IQR)	42 (30, 60)	42 (30, 60)	45 (32, 58)	0.732	44 (30, 60)	40 (30, 60)	0.538
COPD characteristics							
Use of supplemental oxygen, n (%)	91 (41)	82 (41)	9 (50)	0.598	87 (43)	4 (24)	0.182
Persistent cough, n (%)	104 (47)	92 (46)	12 (67)	0.141	92 (45)	12 (71)	0.080
Persistent phlegm, n (%)	122 (55)	109 (54)	13 (72)	0.213	109 (54)	13 (76)	0.119
Post-BD FEV ₁ /FVC ratio, median (IQR)	0.51 (0.39, 0.59)	0.51 (0.40, 0.59)	0.42 (0.36, 0.64)	0.610	0.50 (0.39, 0.59)	0.56 (0.40, 0.60)	0.420
Post-BD FEV ₁ % predicted, median (IQR)	46 (34, 60)	46 (35, 60)	39 (27, 57)	0.169	46 (34, 60)	47 (38, 61)	0.650
GOLD classification of airflow obstruction, n (%)							
GOLD 2: FEV ₁ : 50 – 79% predicted	99 (45)	92 (46)	7 (39)	0.215	91 (45)	8 (47)	0.984
GOLD 3: FEV ₁ : 30 – 49% predicted	81 (37)	76 (38)	5 (28)		75 (37)	6 (35)	
GOLD 4: FEV ₁ :< 30% predicted	40 (18)	34 (17)	6 (33)		37 (18)	3 (18)	

Six-minute walk distance, feet, median (IQR)	1165 (909, 1375)	1165 (913, 1378)	1162 (834, 1350)	0.524	1165 (900, 1370)	1187 (951, 1414)	0.894
Median age of COPD onset, median (IQR)	54 (47, 62)	55 (47, 62)	50 (44, 57)	0.090	55 (48, 62)	48 (44, 57)	0.030
ER visits/hospitalizations in 12 months, n (%)	65 (30)	57 (28)	8 (44)	0.204	59 (29)	6 (35)	0.792
Oral corticosteroid for COPD in 12 months, n (%)	94 (43)	85 (42)	9 (50)	0.687	89 (44)	5 (29)	0.368
Antibiotic for COPD in 12 months, n (%)	101 (46)	89 (44)	12 (67)	0.110	94 (46)	7 (41)	0.877
SABA use, n (%)	166 (75)	149 (74)	17 (94)	0.095	151 (74)	15 (88)	0.326
SAMA use, n (%)	23 (10)	19 (9)	4 (22)	0.193	20 (10)	3 (18)	0.551
SABA and SAMA use, n (%)	21 (10)	17 (8)	4 (22)	0.136	21 (10)	0 (0)	0.335
LAMA use, n (%)	123 (56)	115 (57)	8 (44)	0.439	113 (56)	10 (59)	>0.999
ICS/LABA, ICS or LABA use, n (%)	166 (75)	154 (76)	12 (67)	0.536	152 (75)	14 (82)	0.693
Depression/anxiety characteristics							
MINI diagnosis of anxiety, n (%)	17 (8)	12 (6)	5 (28)	0.004			
MINI diagnosis of depression, n (%)	18 (8)				13 (6)	5 (29)	0.004
Use of any anxiety medications, n (%)	32 (15)	28 (14)	4 (22)	0.538	25 (12)	7 (41)	0.004
Use of any depression medications, n (%)	43 (20)	36 (18)	7 (39)	0.064	35 (17)	8 (47)	0.008
Mental health therapy/counseling, n (%)	22 (10)	18 (9)	4 (22)	0.163	14 (7)	8 (47)	<0.001

*Depression/anxiety disorders meeting the MINI diagnostic criteria

6MWD: 6-minute walk distance; AECOPD: Acute exacerbation of COPD; BD: Bronchodilator; COPD: Chronic obstructive pulmonary disease; ER: Emergency room; FEV₁: Forced expiratory volume in 1 second; FVC: Forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: Inhaled corticosteroid; IQR: Interquartile range; LABA: Long-acting beta agonist; LAMA: Long-acting muscarinic agonist; MINI: Mini-International Neuropsychiatric Interview; SABA: Short-acting beta agonist; SAMA: Short-acting muscarinic agonist

Table 2. Patient-reported symptoms and cognitive assessment among COPD patients with and without depression or anxiety disorders

Questionnaires	Current depression*		p-value	Current anxiety*		p-value
	No (n = 202)	Yes (n = 18)		No (n = 203)	Yes (n = 17)	
MMRC, median (IQR) ↓	3 (1, 4)	4 (3, 4)	0.045	3 (2, 4)	4 (2, 5)	0.059
CAT ↓	17 (12, 24)	27 (20, 30)	<0.001	17 (12, 24)	24 (19, 29)	0.001
PSQI ↓	7 (5, 11)	11 (8, 15)	0.001	7 (5, 11)	10 (8, 13)	0.003
EQ-5D ↑	0.59 (0.36, 0.83)	0.31 (0.12, 0.44)	<0.001	0.59 (0.36, 0.83)	0.40 (0.26, 0.41)	0.003
MoCA ↑	25 (23, 27)	25 (21, 26)	0.106	25 (23, 27)	26 (23, 28)	0.453
GAD-7 ↓	2 (0, 4)	10 (5, 13)	<0.001	2 (0, 4)	10 (6, 13)	<0.001
HADS anxiety ↓	3 (1, 6)	11 (6, 14)	<0.001	3 (1, 6)	11 (7, 13)	<0.001
PHQ-9 ↓	3 (1, 7)	11 (10, 15)	<0.001	4 (1, 7)	9 (7, 12)	<0.001
HADS depression ↓	4 (1, 6)	10 (5, 12)	<0.001	4 (2, 7)	7 (4, 11)	0.002
PROMIS-29 physical function ↑	39 (34, 43)	34 (34, 37)	0.002	37 (34, 43)	36 (33, 40)	0.121
PROMIS-29 anxiety ↓	48 (40, 56)	58 (56, 63)	<0.001	48 (40, 56)	60 (56, 61)	<0.001
PROMIS-29 depression ↓	49 (41, 56)	60 (49, 66)	<0.001	49 (41, 56)	62 (56, 66)	<0.001
PROMIS-29 fatigue score ↓	51 (46, 59)	62 (56, 65)	<0.001	51 (46, 59)	60 (53, 65)	0.001
PROMIS-29 sleep disturbance ↓	51 (44, 56)	58 (54, 64)	<0.001	51 (44, 56)	52 (51, 60)	0.036
PROMIS-29 social ↑	44 (42, 48)	41 (39, 44)	<0.001	44 (42, 48)	44 (41, 44)	0.087
PROMIS-29 pain interference ↓	54 (42, 61)	61 (56, 65)	0.008	54 (42, 61)	61 (54, 65)	0.002
PROMIS-29 pain intensity ↓	2 (0, 5)	5 (2, 7)	0.063	2 (0, 5)	6 (4, 8)	0.003

*Depression/anxiety disorders meeting the MINI diagnostic criteria

↑ Indicates that higher scores are more favorable. ↓ Indicates that lower scores are more favorable.

MINI: Mini-International Neuropsychiatric Interview

MMRC: Modified Medical Research Council Dyspnea Score. Score range 1-5.

CAT: COPD Assessment Test. Score range 0-40.

PSQI: Pittsburgh Sleep Quality Index. Score range 0-21.

EQ-5D: EuroQol-5D-5L. Score range 0-1.

MoCA: Montreal Cognitive Assessment. Score range 0-30.

GAD-7: General Anxiety Disorder-7. Score range 0-21.

HADS: Hospital Anxiety and Depression Scale. Score range 0-21.

PHQ-9: Patient Health Questionnaire for Depression and Anxiety. Score range 0-27.

PROMIS-29: Patient-reported outcomes measurement information system. Scores translated into T-score (mean of 50; standard deviation of 10).

Pre-proof

Table 3. Prevalence of specific anxiety diagnoses meeting MINI diagnostic criteria

Diagnosis	Overall (n=220)	Current depression		p value
		No (n = 202)	Yes (n = 18)	
Any current anxiety disorder, n (%)	17 (8)	12 (6)	5 (28)	0.004
Panic disorder, n (%)	6 (3)	5 (3)	1 (6)	0.989
Agoraphobia, n (%)	10 (5)	7 (4)	3 (17)	0.047
Social anxiety disorder, n (%)	3 (1)	2 (1)	1 (6)	0.589
Post-traumatic stress disorder, n (%)	6 (3)	3 (2)	3 (17)	0.002
Generalized anxiety disorder, n (%)	4 (2)	3 (2)	1 (6)	0.750

MINI: Mini-International Neuropsychiatric Interview (MINI)