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Symptoms of Anxiety and Depression and Use of Anxiolytic-Hypnotics and Antidepressants in Current and Former Smokers with and without COPD - A Cross Sectional Analysis of the COPDGene Cohort

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AUTHOR CONTRIBUTIONS

ASI and **KFH** take full responsibility for the study as a whole including conception and design of the study, data analysis, and manuscript preparation.

ASI, **KFH**, **GLK**, **FSW**, and **MRJ** contributed to coding of psychiatric medication data.

KEH, **SPB**, **VK**, **GLK**, **FSW**, **MRJ**, **EAR**, **HFA**, **KEL**, **CHM**, **MTD**, **MGF**, **GS**, **NAH**, **RAW**, and **BJM** contributed to interpretation of the data and drafting of the manuscript.

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Abstract

Objectives: To compare the frequency of anxiety/depressive symptoms and use of anxiolytic-hypnotics/antidepressants in smokers with and without COPD and to identify characteristics associated with having unmedicated symptoms.

Methods: Cross-sectional analysis of ambulatory, current/former smokers ≥10 pack years enrolled in the COPDGene study. We measured anxiety/depressive symptoms using the Hospital Anxiety and Depression Scale (subscales ≥8), recorded anxiolytic-hypnotic/antidepressant use, and defined unmedicated symptoms as elevated anxiety/depressive symptoms and not on medications. Regression analysis identified characteristics associated with having unmedicated symptoms.

Key Results: Of 5331 current/former smokers (45% with and 55% without COPD), 1332 (25.0%) had anxiety/depressive symptoms. Anxiety symptoms were similar in frequency in smokers with and without COPD (19.7% overall), while depressive symptoms were most frequent in severe-very severe COPD at 20.7% (13.1% overall). In the entire cohort, 1135 (21.2%) were on medications. Anxiolytic-hypnotic use was highest in severe-very severe COPD (range 7.6% −12.0%), while antidepressant use showed no significant variation in smokers with and without COPD (range 14.7%−17.1%). Overall, 881 (66% of those with symptoms) had unmedicated symptoms, which was associated with African American race (adjusted OR 2.95, 95% CI 2.25–3.87), male gender (adjusted OR 1.93, 95% CI 1.57–2.36), no health insurance (adjusted OR 2.38, 95% CI 1.30–4.35), severe-very severe COPD (adjusted OR 1.48, 95% CI 1.04–2.11), and higher respiratory symptoms/exacerbation history (adjusted OR 2.21, 95% CI 1.62–3.02).

Conclusions: Significant unmet mental health care needs exist in current and former smokers with and without COPD. One in five have unmedicated symptoms, identified by key demographic and clinical characteristics.

Keywords

clinical epidemiology; pulmonary diseases; mental health; access to care; population health; smoking; chronic obstructive pulmonary disease; anxiety; depression; antidepressive agents; antianxiety agents

INTRODUCTION

Anxiety and depression affect nearly one in five adults and are the leading cause of disease burden in the United States(1). Anxiety and depressive symptoms are elevated in chronic

obstructive pulmonary disease (COPD)(2, 3) and are also believed to go unrecognized in smokers at risk for COPD(4–7). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging system categorizes smokers into those with and without COPD and provides an ideal framework to compare anxiety and depressive symptoms in the context of anxiolytic-hypnotic/antidepressant use, which has not previously been examined. Characteristics associated with having anxiety or depressive symptoms but not using medications have also not been explored in this population.

Half of adults with anxiety and depression do not receive pharmacologic treatment, and racial disparities exist in access to mental health services nationwide(8–12). Smokers are especially subject to biological and socioeconomic factors that contribute to a high frequency of anxiety and depressive symptoms compared to non-smokers(5, 13, 14), and it is likely that unmedicated symptoms are also a significant problem in smokers. Anxiolytic-hypnotics and antidepressants in conjunction with psychotherapy are the cornerstone of therapy for anxiety and depression in the general population(15), and antidepressants are standard of care for those with severe symptoms(16). However, in COPD, symptoms of anxiety and depression often overlap with fatigue or dyspnea, thus complicating screening. Furthermore, medication treatment of anxiety in those with impaired lung function and chronic hypercapnia is often impeded by provider concerns about respiratory suppression (17). GOLD guidelines are inconclusive regarding the pharmacologic treatment of anxiety and depressive symptoms in COPD(18), and the paucity of data on pharmacologic treatment in the broader population of smokers makes it difficult to examine gaps that could exist between general population guidelines and clinical practice in smokers with and without COPD.

We analyzed data from current and former smokers with and without COPD in the multisite Genetic Epidemiology of COPD (COPDGene) study which was designed to discover genetic factors that contribute to the development of COPD(19). We compared the frequency of anxiety symptoms, depressive symptoms, and use of commonly prescribed anxiolytic-hypnotics and antidepressants across GOLD severity stages, including participants with a history of smoking without COPD. We then identified demographic and clinical characteristics associated with having unmedicated symptoms. We hypothesized that anxiety symptoms, depressive symptoms, anxiolytic-hypnotic use, and antidepressant use would be highest in smokers with COPD compared to those without COPD. We also hypothesized that demographic characteristics such as African American race and clinical characteristic such as higher respiratory symptom burden would identify smokers at increased risk for having unmedicated symptoms.

METHODS

Participants

We analyzed data from the Genetic Epidemiology Study of COPD (COPDGene), which has been previously described(19). The COPDGene study recruited current and former smokers (≥10 pack-years) from 21 centers across the United States. This analysis used data from participants with available Hospital Anxiety and Depression Scale (HADS) and psychiatric

medication data collected only during a Phase 2 study visit. The Institutional Review Board at all sites approved the study, and participants provided written informed consent.

Defining Symptoms and Medication Use

The HADS is a self-administered questionnaire with anxiety (HADS-A) and depression (HADS-D) subscales, each comprised of 7 items rated on a 4-point Likert scale (0 to 3)(20). HADS subscale scores range from 0 to 21, with higher scores indicating more severe symptoms. A score ≥8 on each subscale is the most commonly used threshold for clinically elevated anxiety or depressive symptoms(21). This threshold is associated with clinically important COPD outcomes including exacerbations and identifies anxiety and depression by standardized neuropsychiatric interview with acceptable sensitivity and specificity(22, 23).

Subjects reported current use of psychiatric medications by generic and/or trade names. After pharmacist (MJ) adjudication, members of the study team (FW, KH, ASI, GK) developed the coding scheme used in this analysis. We organized medications by mechanism of action into “commonly prescribed anxiolytic-hypnotics” and “commonly prescribed antidepressants” as follows: commonly prescribed anxiolytic-hypnotics (Lorazepam, Flurazepam, Triazolam, Clonazepam, Chlordiazepoxide, Temazepam, Oxazepam, Clorazepate, Diazepam, Alprazolam, Quazepam, Estazolam); commonly prescribed antidepressants (Selective Serotonin Reuptake Inhibitors [SSRIs] and Serotonin-Norepinephrine Reuptake Inhibitors [SNRIs])(24). SSRIs included Citalopram, Escitalopram, Fluvoxamine, Paroxetine, Fluoxetine, Sertraline, and Fluoxetine/Olanzapine. SNRIs included Duloxetine, Venlafaxine, Levomilnacipran, Desvenlafaxine, and Milnacipran. We performed the analysis with and without the Norepinephrine-Dopamine Reuptake Inhibitor, Bupropion, as it is routinely used for tobacco cessation.

We referred to commonly prescribed anxiolytic-hypnotics or antidepressants as “Medications”. We categorized subjects without currently elevated symptoms of anxiety or depression and who were not on medications as having “No Evidence of Anxiety or Depression”. We categorized subjects “On Medications” as either having “Unsuccessful Medication Treatment” (on medications with elevated symptoms) or “Successful Medication Treatment” (on medications without elevated symptoms). We defined subjects with elevated anxiety or depressive symptoms but not taking medications as having “Unmedicated Symptoms” (Figure 1).

Other Measures

We included only participants with available post-bronchodilator spirometry and categorized participants by GOLD stage as COPD [GOLD I-II (mild-moderate COPD) and GOLD III-IV (severe-very severe COPD)] or no COPD [GOLD 0 (FEV_1/FVC ≥0.70 and FEV_1 %-predicted ≥0.80) and GOLD PRISm (Preserved Ratio Impaired Spirometry or FEV_1/FVC ≥0.70 with FEV_1 %-predicted <0.80)(25)]. We defined low functional status as <350 meters on the six-minute walk test, which has been associated with increased risk for mortality(26). We defined low income as a household income <$15,000 per year(27) and health insurance as categorical. Access to ambulatory preventative care was self-reported as having access to preventative care provided in the outpatient setting rather than in the hospital. We reviewed

comorbidities and generated a comorbidity count (28), including coronary artery disease, angina, heart attack, coronary artery bypass surgery, angioplasty, diabetes mellitus, congestive heart failure, stroke, transient ischemic attack, osteoarthritis, osteoporosis, compression fractures in the back, hypertension, hyperlipidemia, gastroesophageal reflux disease, stomach ulcers, obesity (body mass index ≥30), obstructive sleep apnea, hay fever, and peripheral vascular disease. We categorized participants into groups according to the 2017 GOLD "ABCD" assessment tool, which includes the modified Medical Research Council (mMRC) dyspnea scale (≥2) or the COPD Assessment Test (≥10) and a history of exacerbations in the past year (18). Group D participants have the highest symptom burden and frequency of exacerbations, especially those requiring hospitalizations (Table 2).

Statistical Analysis

We documented adherence to STROBE statement (STrengthening the Reporting of OBservational studies in Epidemiology)(29) in the online supplement (Appendix Table A.1). We reported frequency for categorical variables and mean ± standard deviation (SD) for continuous variables. We compared the frequency of elevated anxiety symptoms, depressive symptoms, use of commonly prescribed anxiolytic-hypnotics or antidepressants, and unmedicated symptoms across the entire cohort using an Omnibus Chi-square test at $p<0.05$ followed by post-hoc group-by-group comparisons between each GOLD stage and by GOLD ABCD groups. We compared differences in characteristics between subjects with unmedicated symptoms to those on medications using Chi-squared test for categorical variables and independent t-test for normally distributed continuous variables or Mann-Whitney U test for non-normally distributed continuous variables.

To identify characteristics independently associated with having unmedicated symptoms, we developed a mixed effects logistic regression model using the *GenLinMixed* function of Statistical Package for the Social Sciences (SPSS 23.0, SPSS Inc., Chicago, IL, USA) and varied the intercept of the model randomly by study center to account for site-specific differences in recruitment(30). Informed by the biopsychosocial model and prior literature, we included clinically important fixed effects that represented spheres of biological, clinical, and socioeconomic characteristics in the full model(31–34). All tests were two-sided, missing data were treated as missing, and we defined an alpha<0.05 as significant.

Role of the Funding Source

The COPDGene Study is supported by the National Institutes of Health and the COPD Foundation, and neither contributed to the design or conduct of this study.

RESULTS

Cohort Description

Of 6125 participants from the COPDGene study, 5997 (97.9%) had medication data available for coding. We excluded 143 (2.4%) subjects with home or phone visits only, 321 (5.4%) never smokers, 65 (1.1%) participants without six-minute walk test data due to safety reasons, 115 (2.0%) who did not have post-bronchodilator spirometry, and 22 (0.04%) with missing weight or smoking data (Figure 1). The current analysis included 5331 participants.

The overall cohort had a mean ±SD age of 65.5±8.6 years, with 2683 (50.3%) males, nearly one third non-Hispanic African Americans, and one third current smokers (Table 1). Overall, 54.8% of participants did not have COPD [GOLD 0 and PRISm], while the remaining 45.1% had COPD [GOLD I-II and GOLD III-IV] (Table 1).

Symptoms and Use of Commonly Prescribed Medications

Overall, 1332 (25.0%) subjects reported elevated anxiety/depressive symptoms [n=1052 (19.7%) with HADS-Anxiety ≥8; n=696 (13.1%) with HADS-Depression ≥8; and n=416 (7.8%) with comorbid anxiety and depressive symptoms]. Frequency of medication use is shown in Table 1. Of the 1332 participants with anxiety or depressive symptoms, 881 (66.1%) had unmedicated symptoms, which represented 16.5% of the overall cohort (Figure 1 and Table 1).

Symptoms and Medications Across GOLD Stages and ABCD Groups

Anxiety symptoms were frequent in all GOLD stages with little variation (GOLD 0: 19.5%; GOLD PRISm: 22.2%; GOLD I-II: 17.9%; and GOLD III-IV: 22.2%, p=0.03). In contrast, the frequency of depressive symptoms differed by GOLD stage (Figure 2). The highest frequency of depressive symptoms occurred in participants with severe-very severe COPD (GOLD 0: 10.4%; GOLD PRISm: 16.5%; GOLD I-II: 11.6%; and GOLD III-IV: 20.7%, p<0.001).

Anxiolytic-hypnotic use differed significantly across GOLD stages (GOLD 0: 7.6%; GOLD PRISm: 8.3%; GOLD I-II: 7.7%; and GOLD III-IV: 12.0%, p<0.001) but there was no significant variation in the frequency of antidepressant use (GOLD 0: 17.1%; GOLD PRISm: 16.2%; GOLD I-II: 15.4%; and GOLD III-IV: 14.7%, p=0.35). Finally, the frequency of unmedicated symptoms differed across GOLD stages, with the highest frequency in GOLD PRISm and GOLD III-IV stage COPD (GOLD 0: 15.3%; GOLD PRISm: 19.2%; GOLD I-II: 15.2%; and GOLD III-IV: 20.4%, p<0.001, Figure 2).

As shown in Table 2, anxiety symptoms were significantly more frequent in GOLD groups B, C, and D than group A (A: 9.2%; B: 29.2%; C: 24.6%; and D: 26.6%, p<0.001), while depressive symptoms were significantly more frequent in GOLD groups B and D than in groups A or C (A: 3.8%; B: 23.6%; C: 14.1%; and D: 19.7%, p<0.001). Anxiolytic-hypnotic use was most frequent in GOLD group D (A: 6.0%; B: 9.3%; C: 8.8%; and D: 12.4%, p<0.001), as was antidepressant use (A: 14.3%; B: 17.2%; C: 15.3%; and D: 20.0%, p=0.001).

Characteristics Associated with Unmedicated Symptoms

Along with the random effect of study center, we included the following clinically important variables based on the biopsychosocial model and the literature as fixed effects in the full model: age, gender, race, income, health insurance, preventative care, GOLD severity stages (reference GOLD 0), GOLD ABCD groups (reference group A), comorbidity count, chronic bronchitis, current smoking, supplemental oxygen, and six-minute walk distance <350 meters. Demographic characteristics that were associated with an increased risk of having unmedicated symptoms versus being on medications included: African American race

(Adjusted OR 2.95, 95% CI 2.25–3.87, $p<0.001$), male gender (Adjusted OR 1.93, 95% CI 1.57–2.36, $p<0.001$), lack of health insurance (Adjusted OR 2.38, 95% CI 1.30–4.35, $p=0.005$), and no ambulatory preventative care (Adjusted OR 1.70, 95% CI 1.07–2.73, $p=0.03$) (Figure 3 and Appendix Table A.2). Clinical characteristics associated with an increased risk for having unmedicated symptoms included having GOLD III-IV stages of COPD (GOLD 0=reference; adjusted OR 1.48, 95% CI 1.04–2.11, $p=0.03$) and higher GOLD ABCD groups, with the highest risk for unmedicated symptoms in group B (reference group A; adjusted OR 2.21, 95% CI 1.62–3.02, $p<0.001$). We re-ran the analyses including Bupropion, a medication comonly prescribed for smoking cessation, and only GOLD III-IV stages lost statistical significance ($p=0.32$).

DISCUSSION

We found that significant unmet mental health care needs exist in smokers with and without COPD. In particular, significant variation exists in the frequency of depressive symptoms and the use of commonly-prescribed anxiolytic-hypnotics across GOLD severity stages. This is the first demonstration that specific subgroups of smokers are at an increased risk for having unmedicated symptoms of anxiety and depression, and the data could aid stratification of those at highest risk for having unmedicated symptoms.

We demonstrated that 25% of smokers in the COPDGene cohort have anxiety or depressive symptoms. Considering symptoms and medication use together, 38% of current and former smokers had some evidence of anxiety and depression, which is similar to other smoker populations(2, 35). Our data reveal a discordance between the frequency of symptoms and the use of medications to treat those symptoms across GOLD stages, including smokers without COPD. Anxiety symptoms are prevalent in all GOLD stages; however, depressive symptoms disproportionately affect smokers in GOLD PRISm and GOLD III-IV stages. Not assessing anxiety and depressive symptoms in smokers without COPD misses those from GOLD 0 and GOLD PRISm stages who also have emotional symptoms. On the other hand, GOLD ABCD grouping, which accounts for dyspnea, quality of life, and exacerbation history, may provide a more effective way of discerning smokers with symptoms of anxiety and depression. We found that anxiety symptoms are over three times more frequent in GOLD groups B, C, and D compared to group A, and depressive symptoms are six times more frequent in GOLD group D compared to group A. The magnitude of differences in psychological symptoms and medication use between GOLD groups were greater than we initially hypothesized, and future studies should validate this finding.

Overall, 8% of the cohort was on a commonly-prescribed anxiolytic-hypnotic, while 16% was on a commonly-prescribed antidepressant. Existing literature raises concerns that benzodiazepine use may cause respiratory suppression or adverse outcomes in COPD, particularly in older patients and those with chronic hypercapnia, which may limit use of benzodiazepines(36–38). GOLD guidelines mention these concerns but do not provide conclusive recommendations regarding pharmacologic treatment of anxiety and depressive symptoms in smokers(18). The data confirm our initial hypothesis that gaps between mental healthcare guidelines and clinical practice exist.

Anxiolytic-hypnotics provide quick relief of anxiety symptoms, and the distress associated with worsening dyspnea may explain, in part, why anxiolytic-hypnotics are more frequent in severe-very severe COPD and in group D (39). We found that anxiolytic-hypnotics are prescribed at nearly twice the frequency in these groups. Guidelines instead recommend SSRIs and SNRIs for sustained control of both anxiety and depressive symptoms in general populations(16, 24), and recent data suggest that SSRIs and SNRIs improve adherence to COPD inhalers(24, 40). We discovered a higher frequency of depressive symptoms without an increased frequency of antidepressant use in those with severe-very severe COPD. Reasons for this are likely multifactorial including lack of awareness of treatment recommendations, provider inexperience initiating and titrating antidepressants in smokers, or bias that symptoms of depression are expected in the context of advanced illness(15, 41). Depressive symptoms in severe-very severe COPD may be due to patients' reaction to loss of function; however, in depression following a major life loss, antidepressant medications successfully improve symptoms(42). Our data support this in that 60.2% of smokers on medications did not report elevated anxiety or depressive symptoms (Figure 1). Future work is needed to examine why antidepressant use does not match the higher frequency of symptoms in severe to very severe COPD and GOLD PRISm.

Unmedicated symptoms affected nearly one in five smokers, or one in three who had elevated anxiety or depressive symptoms in our cohort. Lack of health insurance was associated with a high risk for not receiving medication treatment in the context of elevated anxiety or depressive symptoms. Prior data have shown that the uninsured are at an increased risk for having anxiety and depression(43) and that mental health-related outcomes improve for these patients after expansion of health insurance coverage, likely related in part to reduced constraints and expanded range of available mental health services when insured(44–46). We also discovered that significant racial and gender disparities in unmet mental healthcare needs exist in smokers. Though we were limited by the lack of data on Hispanics in the COPDGene study, our results are consistent with other studies showing that African Americans have a significantly lower utilization of mental health care services(12, 47). The association between male gender and unmedicated symptoms may indicate a degree of stigma, stoicism regarding emotional symptoms, lack of access to mental health services for men in particular (12, 47).

We must consider several limitations in this analysis. First, we did not have information about anxiety or depression diagnoses. Instead, we used a self-reported measure of anxiety and depressive symptoms that is commonly used in patients with COPD and has been examined in multiple settings(22, 48). Second, we did not have access to data on psychotherapy or palliative care, and the rate of referral to cardiopulmonary rehabilitation was low (6.7%). Furthermore, we did not know the specific indication for a psychiatric medication, and it is possible that subjects may have previously tried psychiatric medications, did not report medication use, or were noncompliant. Self-report may have thus introduced recall bias. Still, medications are a cornerstone of treatment for elevated anxiety and depressive symptoms, and no large cohort studies to date have reported the frequency of psychiatric medication use among current and former smokers with and without COPD nor done so in the context of elevated anxiety and depressive symptoms. Our clear approach to classifying medications into commonly-prescribed anxiolytic-hypnotics and

antidepressants(10) is a key contribution of the manuscript that is clinically relevant, maximizes likelihood that participants took these medications for psychiatric conditions, is generalizable, and influences future trial designs. Our results fill gaps in the literature and identify a subpopulation of smokers at highest risk for not receiving medication treatment and may benefit from further assessment.

CONCLUSIONS

Significant unmet mental healthcare needs exist in smokers especially those with severe-very severe COPD and with higher symptom burden or exacerbation history. Smokers from all GOLD severity stages struggle with anxiety symptoms, but a discordance exists in that those with severe-very severe COPD have the highest frequency of depressive symptoms yet receive the highest frequency of anxiolytichypnotics. One in five current and former smokers have unmedicated symptoms, and demographic and clinical characteristics identify those at greatest need. Future studies investigating the impact of unmedicated symptoms on disease outcomes are warranted.

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Appendix Table A.1.: STROBE Statement - Checklist of Items That Should be Included in Reports of Cohort Studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (p. 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (pp. 4–5)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (p. 6)
Objectives	3	State specific objectives, including any prespecified hypotheses (P-7)
Methods		
Study design	4	Present key elements of study design early in the paper (pp. 7–8)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (p. 7–8)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up, (pp. 7–8)
		(b) For matched studies, give matching criteria and number of exposed and unexposed (n/a)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (pp. 8–10)
Data sources/measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group, (pp. 8–11)
Bias	9	Describe any efforts to address potential sources of bias (pp. 10–11)
Study size	10	Explain how the study size was arrived at (pp. 8–10)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. (p.10–11)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (pp. 10–11)
		(b) Describe any methods used to examine subgroups and interactions (pp. 10–11)
		(c) Explain how missing data were addressed (p.11)
		(d) If applicable, explain how loss to follow-up was addressed (n/a)
		(e) Describe any sensitivity analyses (n/a)
Results		
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed (p. 11)
		(b) Give reasons for non-participation at each stage (n/a)
		(c) Consider use of a flow diagram (Figure 1)
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (p. 11)
		(b) Indicate number of participants with missing data for each variable of interest (p. 11)
		(c) Summarize follow-up time (eg, average and total amount) (n/a)

	Item No	Recommendation
Outcome data	15	Report numbers of outcome events or summary measures over time (pp. 11–13)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (Appendix Table 2)
		(b) Report category boundaries when continuous variables were categorized (pp. Table 1)
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (n/a)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (pp. 11–13)
Discussion		
Key results	18	Summarize key results with reference to study objectives (pp. 14–15)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (pp. 17–18)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (p. 17–18)
Generalizability	21	Discuss the generalizability (external validity) of the study results (p. 17–18)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (pp. 11,19)

Appendix Table A.2.: Characteristics Associated with Unmedicated Anxiety or Depressive Symptoms as Compared to Being on Medications – A Mixed Effects Logistic Regression Model (n=2016)

	Unadjusted OR (95% CI)	*p* Value	Adjusted OR (95% CI)	*p* Value
Age (Years)	0.96 (0.95–0.97)	<0.001	1.00 (0.99–1.01)	0.98
African American Race	4.00 (3.25–4.92)	<0.001	2.95 (2.25–3.87)	<0.001
Male Gender	1.99 (1.66–2.38)	<0.001	1.93 (1.57–2.36)	<0.001
Income <$15,000	2.13 (1.78–2.57)	<0.001	1.15 (0.91–1.45)	0.24
No Health Insurance	5.08 (2.94–8.72)	<0.001	2.38 (1.30–4.35)	0.005
No Ambulatory Preventative Care	4.15 (2.74–6.30)	<0.001	1.70 (1.07–2.73)	0.03
GOLD PRISm *	1.27 (0.96–1.67)	0.09	1.08 (0.78–1.48)	0.65
GOLD I-II *	1.06 (0.86–1.32)	0.59	1.12 (0.87–1.45)	0.38

	Unadjusted OR (95% CI)	*p* Value	Adjusted OR (95% CI)	*p* Value
GOLD III-IV *	1.32 (1.03–1.70)	0.03	1.48 (1.04–2.11)	0.03
GOLD B †	2.71 (2.12–3.45)	<0.001	2.21 (1.62–3.02)	<0.001
GOLD C †	2.28 (1.75–2.98)	<0.001	1.81 (1.34–2.44)	<0.001
GOLD D †	2.00 (1.54–2.59)	<0.001	1.65 (1.18–2.29)	0.003
Comorbidity Count	0.88 (0.85–0.92)	<0.001	0.93 (0.89–0.97)	0.001
Chronic Bronchitis	1.38 (1.08–1.75)	0.009	1.15 (0.88–1.50)	0.32
Current Smoking	2.29 (1.91–2.74)	<0.001	1.24 (0.98–1.58)	0.07
Supplemental Oxygen	0.75 (0.59–0.96)	0.03	0.76 (0.54–1.06)	0.11
Six-minute Walk Distance <350m	1.18 (0.98–1.41)	0.08	0.86 (0.68–1.10)	0.24

*Reference GOLD 0.

†Reference GOLD Group A.

Notes: Unmedicated Anxiety and Depressive Symptoms = Anxiety/depressive symptoms and not on a commonly prescribed anxiolytic-hypnotic or antidepressant.

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Highlights

- Significant unmet mental healthcare needs exist in current and former smokers.
- Symptoms and treatment of anxiety/depression vary across COPD severity stages.
- One in five smokers have unmedicated anxiety/depressive symptoms.
- Subgroups of smokers are at risk for unmedicated anxiety/depressive symptoms.
- Characteristics identify smokers at highest risk for having unmedicated symptoms.

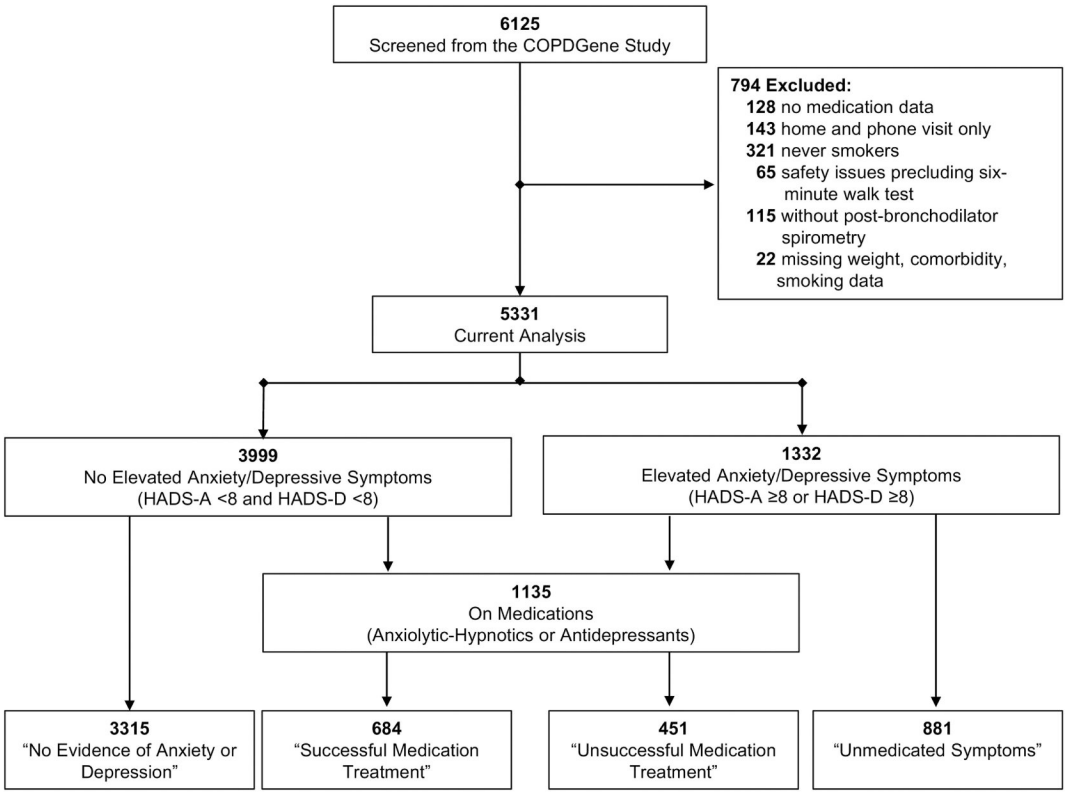

Figure 1. Subjects Screened and Enrolled from the COPDGene Study.

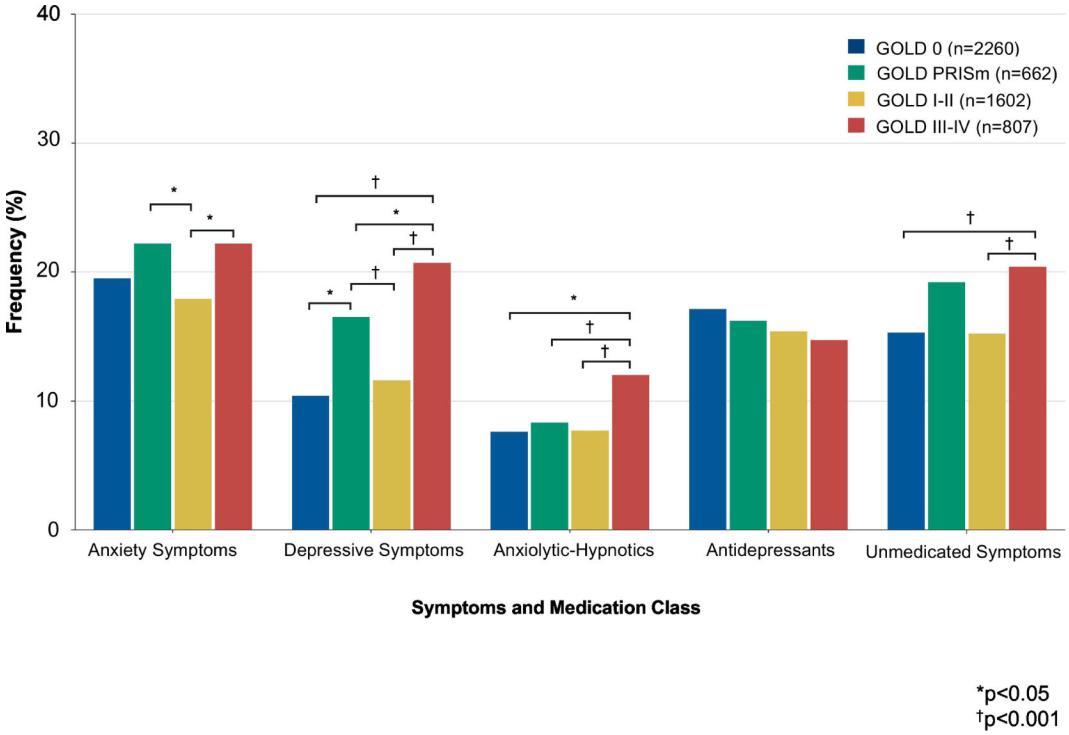

Figure 2. Symptoms of Anxiety and Depression and Use of Anxiolytic-Hypnotics and Antidepressants by GOLD Stage.

Anxiety symptoms, depressive symptoms, anxiolytic-hypnotic use, antidepressant use, and unmedicated symptoms across GOLD severity stages using ANOVA followed by post-hoc group-by-group comparisons. *p<0.05; †p<0.001

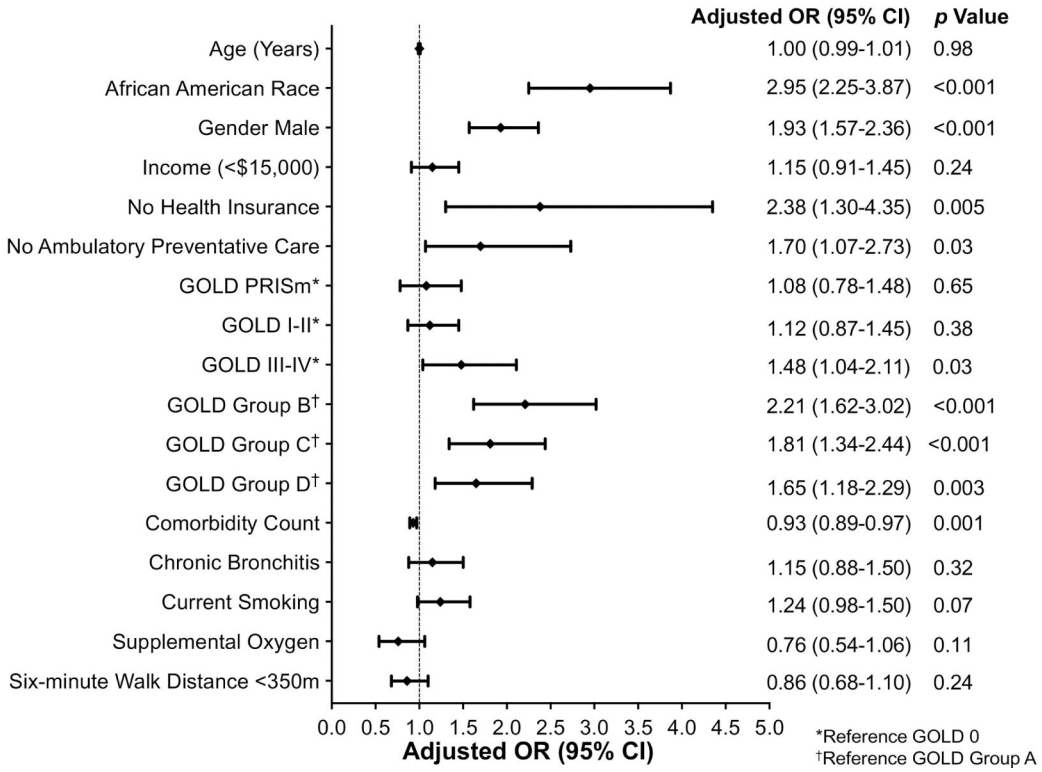

Figure 3. Characteristics Associated with Unmedicated Anxiety or Depressive Symptoms.

Mixed effects logistic regression model with unmedicated symptoms as the dependent variable compared to being on medications, study center as the random effect, and clinically important variables included in the full model. See Appendix 2 for full model. *Reference GOLD 0. †Reference GOLD Group A.

Table 1.

Cohort Demographic and Clinical Characteristics (n=5331)

Variable	*n (%) or Mean ±SD*
Age (Years)	65.5±8.6
Gender (% Male)	2683 (50.3)
Race (% African American)	1573 (29.5)
Income <$15,000 (%)	1432 (26.9)
Health Insurance (%)	5136 (96.3)
Ambulatory Preventative Care (%)	5047 (94.7)
GOLD Stage	
GOLD 0 (%)	2260 (42.4)
GOLD PRISm (%)	662 (12.4)
GOLD I-II (%)	1602 (30.1)
GOLD III-IV (%)	807 (15.1)
Comorbidity Count	3.4±2.4
Current Smoking (%)	2022 (37.9)
Oxygen Therapy (%)	648 (12.2)
No Exercise in Last 3 Weeks (%)	2473 (46.4)
Unintentional Weight Loss (%)	594 (11.1)
Chronic Bronchitis (%)	819 (15.4)
Six-minute Walk Distance (m)	392.4±131.9
Cardiopulmonary Rehabilitation in the Last 5 Years (%)	337 (6.7)
Inhaled bronchodilators (%)	5197 (97.5)
Inhaled corticosteroids (%)	1328 (24.9)
GOLD ABCD Groups *	
Group A	2180 (40.9)
Group B	1239 (23.2)
Group C	1007 (18.9)
Group D	905 (17.0)
Anxiety or Depressive Symptoms	1332 (25.0)
Anxiety Symptoms (HADS-Anxiety ≥8)	1052 (19.7)
Depressive Symptoms (HADS-Depression ≥8)	696 (13.1)
Both Anxiety and Depressive Symptoms	416 (7.8)
Commonly Prescribed Anxiolytic-Hypnotics or Antidepressants	1135 (21.3)
Anxiolytic-Hypnotics	446 (8.4)
Antidepressants	859 (16.1)
Selective Serotonin Reuptake Inhibitors	650 (12.2)
Serotonin-Norepinephrine Reuptake Inhibitors	219 (4.1)
Anxiolytic-Hypnotic and Antidepressant	170 (3.2)
Norepinephrine-Dopamine Reuptake Inhibitor (Bupropion)	224 (4.2)
Unmedicated Symptoms †	*881 (16.5)*

* See Table 2 for classification. GOLD Group D has highest symptom burden and history of frequent exacerbations.

[†]HADS-Anxiety ≥8 or HADS-Depression ≥8 and not an anxiolytic-hypnotic or antidepressant

Abbreviations: GOLD = Global Initiative for Obstructive Lung Disease; PRISm = Preserved Ratio with Impaired Spirometry; HADS = Hospital Anxiety and Depression Scale

Table 2.

Symptoms of Anxiety and Depression and Use of Anxiolytic-Hypnotics and Antidepressants by GOLD ABCD Groups (n=5331)

Exacerbation History	**GOLD ABCD Groups**	
≥2 or ≥1 Leading to Hospital Admission	**C** (n=1007) Anxiety Symptoms: 24.6% Depressive Symptoms: 14.1% Anxiolytic-Hypnotics: 8.8% Antidepressants: 15.3% Unmedicated Symptoms: 19.9%	**D** (n=905) Anxiety Symptoms: 26.6% Depressive Symptoms: 19.7% Anxiolytic-Hypnotics: 12.4% Antidepressants: 20.0% Unmedicated Symptoms: 23.0%
0 or 1 Not Leading to Hospital Admission	**A** (n=2180) Anxiety Symptoms 9:2% Depressive Symptoms: 3.8% Anxiolytic-Hypnotics: 6.0% Antidepressants: 14.3% Unmedicated Symptoms: 7.5%	**B** (n=1239) Anxiety Symptoms 29.2% Depressive Symptoms: 23.6% Anxiolytic-Hypnotics: 9.3% Antidepressants: 17.2% Unmedicated Symptoms: 25.0%
	mMRC 0–1 or CAT<10	mMRC ≥2 or CAT ≥10
	Symptoms	

Abbreviations: mMRC = modified Medical Research Council Dyspnea scale; CAT = COPD Assessment Test