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Articles

Overlap and common correlates between depression and COPD: a narrative review

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is characterized by a burden of comorbid conditions, including depression, that has been related with an increased risk of exacerbations, low adherence to pharmacological treatments and behavioral interventions, and overall mortality rates. The aim of the present review was to explore the comorbidity between depression and COPD by examining epidemiological and etiopathogenetic perspectives, along with shared risk factors including the potential role of hypoxia, systemic inflammation, and drugs for COPD treatment.

Methods: the aim of this work was to review studies published in the last eleven years, using Medline/PubMed, Scopus, and Google Scholar as search engines and the following terms "Mood Disorders", "Hypoxia "Pulmonary Disease, Chronic Obstructive", "Chronic obstructive pulmonary disease", linked by the Boolean operator "AND". Articles were included in the review if written in English and containing quantitative and qualitative information on Depression, Chronic Obstructive Pulmonary Disease, and Hypoxia. Exclusion criteria were studies in languages other than English, irrelevant articles to the examined topic reviews, case reports, case series, and articles on animal models.

Results: The present review has confirmed the increased risk of depression onset in COPD patients, suggesting a strong multifactorial and bidirectional correlation between the two conditions. Hypoxia has been emphasized as a key mechanism in both diseases, whereas evidence on shared inflammatory and molecular pathways is still limited.

Conclusions: The multifactorial nature of the bidirectional correlation between COPD and depression is far from being entirely understood. Comorbid depression negatively affects COPD course and severity, along with patients' functioning, psychological well-being and quality of life. Well-designed pre-clinical and clinical studies on the genetic, molecular, and neurobiological pathways which underlie the comorbidity between COPD and depression are needed for addressing the clinical implications and treatment options. needs more research efforts to be clarified. Further studies are mandatory to improve our knowledge on the co-presence of these two widespread diseases.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease affecting both lower airways and lung parenchyma, characterized by chronic respiratory symptoms such as cough, sputum, dyspnoea and by a progressive and irreversible airway flow obstruction (Cannavò et al., 2022).

COPD development is mediated only by chronic cigarette smoke inhalation, and COPD diagnosis is placed excluding other lung diseases (such as asthma with persistent airflow obstruction, bronchiectasis with chronic airflow obstruction, and previous pulmonary tuberculosis) or lung development abnormalities through an accurate differential diagnostic algorithm to all patients characterized by chronic irreversible airflow obstruction (Cannavò et al., 2022; Gnatiuc & Caramori, 2014; Lange et al., 2015; Thomsen et al., 2013).

COPD patients are usually affected by numerous comorbidities, including mood disorders, mainly depression (Maurer et al., 2008), that has been related with an increased risk of mortality and hospitalizations (Ng, 2007). Rates of depression in COPD patients range from 24.6% to 27.1%, a significant prevalence when compared with depression rates in non-COPD patients, estimated up to 11.7% (Matte et al., 2016; Zhang et al., 2011). According to the revised version of the Diagnostic and Statistical Manual of Mental Disorders, DSM-5 TR, Major Depressive Disorder (MDD) is characterized by recurrent depressive episodes diagnosed through five or more symptoms experienced during the same 2-week period, and at least one of the symptoms should be either depressed mood or anhedonia (American Psychiatric Association, 2022). MDD, which affects nearly 322 million people worldwide (Smith, 2014) with a 12-month prevalence of approximately 6%, overall (Malhi & Mann, 2018), strongly contributes to the global burden of disease as the world leading cause of disability; nevertheless, it continues to be under-recognized and undertreated, especially when it is comorbid with organic illnesses (Kim et al., 2011).

When associated with COPD and other respiratory conditions, physical symptoms of both chronic respiratory disease and depression can overlap, making the diagnosis even more difficult (DeJean et al., 2013). The co-occurrence of depressive disorders in COPD patients has received a certain attention, yet literature data on this topic and on potential shared pathways are still scarce.

Several studies suggest that COPD can increase the risk of depression; this could be partly mediated by the drugs used for treating COPD; it has been shown that systemic glucocorticoids for illness exacerbations, inhaled glucocorticoids (ICS) with or without inhaled bronchodilators, and long acting β_2-agonists and long acting anti-muscarines (LAMA) administered to stable COPD patients can induce mood changes (depression and mania), psychotic symptoms, and memory loss (DeJean et al., 2013; Putman-Casdorph & McCrone, 2009). Furthermore, COPD severity is positively correlated with depression onset and severity, and this is particularly true for severest forms and advanced stages of COPD, characterized by chronic respiratory failures treated with long term oxygen therapy (LTOT); beyond the classical explanation that points at the role of LTOT in worsening quality of life of COPD patients, it should be taken into account that hypoxia can induce depression (Hogea et al., 2020), as suggested by several studies that underlined the potential role of hypoxic injury on neuronal plasticity in the pathogenesis of mood disorders (Zhao et al., 2017). Within this frame, depression may appear as an understandable consequence of COPD; however, it has also been viewed as an independent disease, since a great number of patients experienced depressive episodes before the onset of COPD (Schneider et al., 2010).

In particular, cigarette smoking exposure increases the risk of depression even in smokers with normal lung function, thus representing a shared risk factor for both diseases, depression and COPD (Farr et al., 2011; Mannino & Buist, 2007). Moreover, chronic inflammation can be a further pathogenetic factor shared between the two diseases and involved either in the neurobiological pathway of MDD and in lung abnormal immune response mediating progressive and irreversible airflow limitation in COPD and lung emphysema (Mannino & Buist, 2007). From these perspectives, interactions between chronic smoke exposure, chronic inflammation and hypoxic mechanisms may be common pathways linking depression and COPD (Troubat et al., 2021). COPD involves the degradation of alveolar capillaries and airflow restrictions, inducing hypoxia (Pelgrim et al., 2019); the reduction of arterial oxygen's levels which can cause confusion, altered consciousness, and mental slowing (Levenson, 2007). It has been also shown that both periodic and continuous COPD-related hypoxia in the brain could negatively affect neurotransmitters metabolism in the brain (Thakur et al., 2010). Furthermore, the role of hypoxia-associated oxidative stress has been consistently designated as a key factor in the onset of depressive symptoms (Rose & Sharafkhaneh, 2017). All the above-mentioned mechanisms along with associated low-grade systemic inflammation, might be involved in the onset of brain dysfunctions and psychiatric comorbidities in COPD patients.

The aim of the present review was to explore the comorbidity between depression and COPD by examining epidemiological and etiopathogenetic perspectives, along with shared risk factors including the potential role of hypoxia, systemic inflammation, and drugs for COPD treatment.

2. Methods

2.1 Search strategy

All articles published in the last eleven years on the relationship between depression and COPD, with attention to chronic inflammation and hypoxic mechanisms, have been reviewed.

Studies have been identified through research carried out in Medline/PubMed, Scopus, and Google Scholar using the following keywords: “Mood Disorders", "Hypoxia "Pulmonary Disease, Chronic Obstructive", “Chronic obstructive pulmonary disease”, linked by the Boolean operator “AND”.

2.2 Eligibility criteria

Articles were included in the review according to the following inclusion criteria: articles written in English language, and containing quantitative and qualitative information on Depression, Chronic Obstructive Pulmonary Disease, and Hypoxia. References from the selected articles were also checked.

2.3 Exclusion criteria

Articles were excluded if irrelevant to the examined topic. Reviews, case reports, case-series, and articles on animal models were also excluded.

3. Results

3.1 Depression in patients with COPD

Six articles examined the co-occurrence of depression and COPD (Table 1).

Table 1. Depression in patients with COPD

Reference	Type of study	Subjects	Assessment	Main findings
Hanania et al., 2011	Noninterventional, observational, prospective, 3-year multicenter study (ECLIPSE)	2,118 subjects with COPD; 335 smokers with normal lung function; 243 non-smokers.	Center for Epidemiologic Studies Depression Scale (CES-D)	Depression was present in 26% of subjects with COPD, 12% of smokers with normal lung function and 7% of non-smokers.
Miravitlles et al., 2014	DEPREPOC (Depression in Chronic Obstructive Pulmonary Disease): observational, cross-sectional, multicenter study	Total sample: 836 COPD patients.	Beck Depression Inventory; Mini Mental State Examination (MMSE); EuroQoL-5 dimensions (EQ-5D) questionnaire and the COPD Assessment Test (CAT) for health-related quality of life (HRQoL).	Depression was frequent in COPD and associated with severity of COPD, number of comorbid illnesses, physical inactivity, suicidal ideation, and impaired HRQoL.
Yohannes et al., 2017	Observational study	Total sample: 2059 COPD patients.	Center for Epidemiologic Studies Depression Scale (CES-D)	73.7% (n = 1519) patients reported low depressive symptoms, 26.3% (n = 540) high depressive symptoms. About one in four COPD patients maintained persistent depressive symptoms over 3 years.
Kayhan et al., 2018	Observational study	54 COPD patients (GOLD IV)	Structured Clinical Interview for the DSM-IV – SCID-I/CV; Beck Depression Inventory (BDI)	MDD was found in 63.0% (n=34) patients, and related with noncompliance to long-term oxygen therapy (LTOT).

Xiao et al., 2018	Cross-sectional study	275 COPD patients	Hospital Anxiety and Depression Scale (HAD); EQ-5D visual analogue ($EQ\text{-}5D_{vas}$)	13.1% patients of the total sample. had depression. Anxiety and depression levels were higher in COPD patients living in urban communities.
Pietras et al., 2011	Case-control study	174 COPD patients (154 smokers, 88.21%) vs. 121 age-matched controls (57 active smokers, or ex-smokers, 47.10%)	Clinical diagnosis according to ICD-10; Beck Depression Inventory - BDI	COPD increases 2.7-fold the probability of developing depression; increased risk for depression in severe COPD patients compared to mild/moderate COPD patients.

In the observational, 3-year, multicentre study (Hanania et al. 2011), depression onset was increased in COPD patients compared with both smokers with normal lung function and non-smokers; in addition, depressive symptoms were positively correlated with COPD severity. COPD and depression association was also positively correlated with female gender, smoking habit, history of cardiovascular disease, and enhanced risk of COPD exacerbations and hospitalizations. Moreover, depressive symptoms were correlated with dyspnoea and airflow obstruction, increase of body mass index, fatigue, sedentary lifestyle, and worsening of quality of life indexes. Similarly, Miravitlles et al. (2014) reported that almost three quarters of a large cohort of COPD patients showed depressive symptoms, with up to 51.5% of the sample showing moderate or severe depression related with increased risk of COPD exacerbations, worse quality of life, and suicide ideation. The longitudinal observational study by Yohannes et al. (2017) evidenced persistent depressive symptoms in COPD patients; depression severity was correlated with female gender, younger age, obesity, and current smoking. Major Depression (MD) onset was significantly increased in stable COPD patients with chronic respiratory failure treated with LTOT compared to stable COPD patients without chronic respiratory failure; in addition, further risk of MD onset was found in stable COPD patients with chronic respiratory failure who were non-compliant with LTOT (Kayhan et al., 2018).

Interestingly, risk for depression onset increased in COPD patients living in urban communities and characterized by poor health status (Xiao et al., 2018). Finally, Pietras and colleagues (2011)

have shown that the risk of depression onset is significantly increased in severe COPD patients than in mild/moderate COPD patients and controls

3.2 Depression, COPD and co-influence on outcome and symptoms

Starting from the evidence that depression and other psychiatric disorders may have a substantial impact on the quality of life of COPD patients through limitation of activities, isolation, worse coping styles, tolerance, and adjustment to illness, and interference with sleep, three articles investigated the role of comorbid depression on COPD symptoms and outcome (Table 2).

Table 2. Depression, COPD and co-influence on outcome and symptoms

Reference	Type of study	Subjects	Assessment	Main findings
Doyle et al., 2013	Randomized controlled trial (INSPIRE-II study)	162 COPD patients	Beck Depression Inventory (BDI-II)	High levels of depressive symptoms in 27.8% of the sample
De, 2011	Cross-sectional study	100 COPD patients	Patient health questionnaire-9 (PHQ-9)	Prevalence of all depressions: 72%. Severe depression: 17%.
Iyer et al., 2015	Retrospective observational study	422 patients with COPD exacerbation divided into two subgroups according to the criterion of 1-year readmission; readmitted (n = 132) and non-readmitted (n = 290).	Clinical diagnosis or reports from electronic medical records.	Depression

As shown by results from the randomized, controlled INSPIRE study, both depression and anxiety were associated with increased dyspnoea, shortness of breath, and severity of symptoms in COPD patients (Doyle et al., 2013). Beyond the high rates of cumulative prevalence of depression (major and minor depression), the study by De (2011) showed that 72% COPD patients were depressed, and the presence of depressive symptoms was related with COPD symptoms severity.

The retrospective observational study aimed at evaluating risk factors for either short- (within 30 days and 90 days of index admission) and long-term (within one year) readmissions for COPD exacerbations, showed that depression was associated with increased 30-day readmission; the correlation remained significant also after adjusting for age, race, sex, smoking habit, and other potentially confounding variables (Iyer et al., 2015). Depression was also independently associated with increased risk of 90-day readmission; overall, COPD patients with depression reported more dyspnoea symptoms, worse quality of life, and decreased treatment adherence.

3.3 Risk factors for depression and COPD: smoking, monoamines and inflammatory pathways

Four articles investigated the role of established and potential risk factors for comorbid depression and COPD, such as smoking habit, monoamine levels, and inflammation (Table 3).

Table 3. Risk factors

Reference	Type of study	Subjects	Assessment	Main findings
Lores et al., 2018	Observational, cross-sectional study	276 psychiatric patients admitted to the	Lores et al., 2018	Observational, cross-sectional study
Sekiduka-Kumano et al., 2013	Case control study	Total sample= 106 subjects: 23 non-smokers, 13 smokers with normal lung function, 50 non-depressed and 20 depressed COPD patients.	Centre for Epidemiologic Studies Depression Scale (CES-D);	Sekiduka-Kumano et al., 2013
Janssen et al., 2014	Clinical trial from ECLIPSE study	481 COPD (22.2%) patients out of the rom the original ECLIPSE cohort of 2164 patients	Centre for Epidemiologic Studies Depression Scale (CES-D);	Janssen et al., 2014
Papp et al., 2017	Cross-sectional study	74 COPD patients	Routine laboratory parameters; serum irisin and brain-derived neurotrophic factor (BDNF) levels; St George's	Two subgroups according to Impacts score: lower (<32.65%) Impacts score group (n=40), and higher (≥32.65%) Impacts score

			Respiratory Questionnaire (SGRQ): Impacts score was chosen as indicative of mood disorders and overall psycho-social dysfunction.	group (n=34), Impacts score and the reciprocal of serum irisin were significantly correlated. Body mass index, body weight, log triglyceride, and severity of airflow limitation were significantly associated with mood disturbances among COPD patients.

A cross-sectional, observational study has shown that 155 patients hospitalized for psychiatric disorders including depression, showed high rates of smokers (54% depressed patients) who showed more severe respiratory symptoms such as cough and sputum, than non-smokers; 29% of the total sample were COPD patients (Lores et al., 2018).

Starting from the evidence that functions of monoamine and monoamine oxidase are associated both with depression and with smoking-related diseases, serotonin, epinephrine and norepinephrine metabolites homovanillic acid (HVA), 3-methoxy-4-hydroxyphenylglycol (MHPG), and 5-hydroxyindoleacetic acid (5-HIAA) have been investigated as possible biomarkers of depressed COPD patients by Sekiduka-Kumano et al. (2013). Results showed that depressed patients with COPD had significantly increased plasma 5-HIAA and MHPG levels than nondepressed COPD patients and non-smokers, both depressed and non-depressed; moreover, the plasma 5-HIAA levels were positively correlated with the severity of depression in COPD patients.

In the attempt to elucidate the potential mechanisms underlying mood disorders in COPD, two articles evaluated the potential involvement of inflammation and pro-inflammatory mediators. The role of persistent systemic inflammation (PSI) has been explored by Janssen et al. (2014). PSI has been defined as the presence, at study baseline and after one year follow-up, of increased levels of two or more of the indexed inflammatory biomarkers such as white blood cell (WBC) count, high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and fibrinogen. Results showed that the presence of PSI was not related with clinical symptoms of depression at baseline nor at follow-up, whereas the main determinants of depression in the sample were dyspnoea

and disease-specific health status. Based on the hypothesis that irisin, a contraction-regulated myokine formed by proteolytic cleavage of transmembrane fibronectin type III domain-containing protein 5 (FNDC5), may represent a link between physical activity and reward-related learning and motivation by inducing brain-derived neurotrophic factor (BDNF) expression in the ventral tegmental area (VTA) and hippocampus, Papp et al. (2017) focused on the role of serum irisin and BDNF levels as potential predictors of depression in a cohort of COPD patients. They found that decreased irisin levels were associated with more severe depressive symptoms, and this correlation was even more prominent among patients with lower BDNF levels. Body mass index (BMI), triglycerides levels, and body weight were significantly associated with mood disturbances among COPD patients. The Authors suggested that exercise-induced increase in irisin levels may be beneficial in depressed COPD patients both by promoting weight loss and enhancing mood via activation of the BDNF pathway in those brain centres involved in affective disorders.

4. Discussions

The quality of life of COPD patients is often complicated by concurrent depressive disorders, whose high prevalence proportionally increases with the severity of COPD (Atlantis et al., 2013). Patients with COPD and mood disorders (depression/anxiety) have an increased risk of more frequent and severe COPD exacerbations, often requiring hospitalization; overall, such patients show lower survival rates (Hanania et al., 2011; Kayhan et al., 2018; Wong et al., 2014; Xiao et al., 2018; Yohannes et al., 2017).

In COPD, the inflammatory response involves both innate and adaptive immunity mainly mediated by neutrophils and macrophages (Barnes, 2017). Several proinflammatory mediators such as cytokines and acute phase proteins are involved in psychiatrics diseases, with a fairly unanimous consensus of increases in IL-6, tumor necrosis factor (TNF)□, and C-reactive protein (CRP) in the blood of depressed patients compared to healthy controls (Beurel et al., 2020). The levels of inflammatory mediators in depression may imply a pool of biomarkers shared with other inflammatory chronic disorders, including COPD. However, this hypothesis needs further pre-clinical and clinical investigations. The mechanisms of the association between COPD and depression are still not known. It is possible that COPD, similarly to other chronic and debilitating illnesses burdened by discomfort and functional limitations, facilitates the onset of depression or, in turn, it is also plausible that depression leads to the onset of COPD, either directly or indirectly through the intervention of mediating factors. However, the relationship

between depression and COPD seems to be bidirectional and, probably, multifactorial in its nature (Pietras et al., 2011). COPD severity has been associated with an increased risk for depression; however, depression itself has a chronic course, intrinsically burdened by the recurrency of episodes, thus suggesting that depression is probably not a mere consequence of COPD, but rather an independent disease associated with COPD in a mutual relationship. It has been proposed that the association between COPD and mood disorders may derive either from the effect of inflammatory mediators and from dysfunctional psychological mechanisms, such as coping styles, cognitive biases, and susceptibility to stressors; this hypothesis reinforces the multifactorial basis underlying the connection between COPD and depression (Pietras et al., 2011). For a better understanding of such multifactorial relationship, the identification of shared and common risk factors should be mandatory. According to the reviewed articles, cigarette smoking has been associated with COPD, depression, and other psychiatric disorders. The study by Lores et al. (2018) shows how smoker psychiatric patients presented more respiratory symptoms than non-smokers; in this case smoke is a risk factor for respiratory diseases in psychiatric patients, including those affected by depression, suggesting that smoking habit could be one of the shared factors in depression and COPD. The common mechanism underlying both depression and COPD symptoms could be chronic hypoxia, a clinical condition that has been associated with both respiratory and mood symptoms (McNicholas et al., 2011). The finding of increased plasma monoamine levels in depressed patients with COPD, and their association with hypoxia and hypercapnia, further suggests the key role of hypoxia in the co-occurrence of COPD and depression (Sekiduka-Kumano et al., 2013). The expression of the hypoxia inducible factor-1 (HIF-1), a transcriptional factor that regulates gene expressions in response to decreased oxygen levels in the tissue, is increased in depressed patients vs. controls (Shibata et al., 2013), overexpressed in the lungs of COPD patients, and variants of the HIF-1α gene are associated with an increased risk of COPD (Shukla et al., 2020). All the examined studies lead to the consideration that smoking, together with hypoxia, could be the key factors in the relationship between depression and COPD.

Regarding the hypothesis of the general role of inflammation, the study of Janssen et al. (2014) do not confirm a significant relationship between depression and systemic inflammation in COPD; this is quite conflicting with the evidence on the known role of low-grade inflammation in depression and the evidence of inflammatory signs in COPD, when the two conditions are assessed separately (Birrell & Eltom, 2011; Kohler et al., 2016).

Beyond the still poorly explained role of potential common pathways for both diseases, it is generally confirmed that the presence of a clinically relevant depressive disorder has a significantly affects COPD symptoms severity and outcome.

Furthermore, depression has been indicated as a predictor of mortality during hospitalization due to acute respiratory disease (Pooler & Beech, 2014). Depression significantly impacts on the amount and severity of pulmonary-specific symptoms among patients with COPD (Doyle et al., 2013), and the incidence and severity of depression are proportionally related with COPD severity (De, 2011; Smith & Wrobel, 2014). According to the results from Iyer et al. (2015) depression is an independent risk factor for both short- (30-day and 90-day) and long-term (1-year) readmissions for acute exacerbation of COPD depression; furthermore, patients with COPD and depression show decreased adherence to medical treatments and to behavioral interventions such as smoking cessation and pulmonary rehabilitation.

The observed "independence" of depression highlights the bidirectional relationship between comorbid COPD and depression, suggesting depression as both a cause and a consequence of COPD course with inevitable repercussions on clinical symptoms and quality of life, not differently from other chronic conditions (Maoua et al., 2014).

Finally, there are few data regarding the potential role of commonly used drugs for COPD treatment such as glucocorticoids and inhaled bronchodilators (Caramori et al., 2019; Dubovsky et al., 2012) in the onset and/or worsening of depression. Pharmacological treatment of stable COPD includes long-term use of several inhaled drugs including ICS, β_2-agonists and antimuscarins, in addition to systemically administered glucocorticoids for COPD exacerbations (Cannavò et al., 2022). It is well-known that exogenous glucocorticoids either topic and systemic, via their effects on the hypothalamic-pituitary-axis (HPA), can affect central nervous system functioning (Caramori et al., 2019). It has been shown that long-term administration of glucocorticoids can induce different neuro-psychiatric symptoms and disorders such as insomnia, cognitive impairment, memory loss, mania, psychosis, anxiety, suicidal behavior and delirium (Caramori et al., 2019; De Quervain et al., 2017; Fardet et al., 2012; Ismail et al., 2017; Moraitis et al., 2017; Mourtzi et al., 2021; Raglan et al., 2017). Nevertheless, the glucocorticoid-mediated onset of depression yet remains a matter of debate, since symptoms of depression during glucocorticoid treatments are more frequent in patients with a past and/or actual history of depression (Dubovsky et al., 2012). However, main evidence arise in large measure from studies aimed at evaluating patients with diseases different from COPD, and the potential depressogenic role of inhaled and systemic glucocorticoids for COPD, along with the effect of

inhaled β_2-agonists and antimuscarinics on mood, deserves further pre-clinical and clinical research.

5. Strengths and Limitations

The main limitation is that the model of the narrative review on the available literature provides less reproducibility than a systematic review, although its strength mainly consists in offering a contribute to the knowledge on the complex and multifactorial relationship between depression and COPD.

6. Conclusions

According to the examined evidence, the multifactorial nature of the bidirectional correlation between COPD and depression is far from being entirely understood. Several lines of research highlight the key role of chronic hypoxia, whereas few data support the potential role of shared inflammatory mechanisms, which may represent a promising research target for pathogenesis and treatment options, along with more accurate molecular and genetic approaches. In addition, there are no data about the potential role of the drugs usually administered for COPD treatment in the onset and/or worsening of depression. However, what emerges with clarity from the reviewed literature is the significant incidence and prevalence of depression in COPD patients, as well as its negative impact on COPD symptoms, treatment adherence, exacerbations, and outcome. This well-documented co-occurrence has several implications for treatment guidelines and interventions. Within this combined approach, the evidence-based, guideline-recommended intervention of pulmonary rehabilitation (PR) for the management of COPD should be integrated by specific interventions, either pharmacological in the case of severe MDD, and psychological and or behavioral, such as psychoeducation, psychotherapy, cognitive techniques, and lifestyle changes, aimed at preventing and treating the burden of depressive symptoms and their impact on functioning, psychological well-being and quality of life of COPD patients.

Conflict of interest statement

Authors declare no conflict of interest

Author Contributions

FI and FN: Data curation, Writing- Original draft preparation. GC and MRAM: Conceptualization, Writing- Reviewing and Editing. AB: Visualization, Methodology, Supervision.

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