Review Article

Anxiety and depression—Important psychological comorbidities of COPD

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Abstract: Anxiety and depression are common and important comorbidities in patients with chronic obstructive pulmonary disease (COPD). The pathophysiology of these psychological comorbidities in COPD is complex and possibly explained by common risk factors, response to symptomatology and biochemical alterations. The presence of anxiety and/or depression in COPD patients is associated with increased mortality, exacerbation rates, length of hospital stay, and decreased quality of life and functional status. There is currently no consensus on the most appropriate approach to screening for anxiety and depression in COPD. Treatment options include psychological [relaxation, cognitive behavioural therapy (CBT), self-management] and pharmacological interventions. Although there is some evidence to support these treatments in COPD, the data are limited and mainly comprised by small studies. Pulmonary rehabilitation improves anxiety and depression, and conversely these conditions impact rehabilitation completion rates. Additional high quality studies are urgently required to optimise screening and effective treatment of anxiety and depression in patients with COPD, to enhance complex chronic disease management for these patients.

Keywords: Chronic obstructive pulmonary disease (COPD); anxiety; depression; comorbidities; diagnosis; therapy

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Chronic obstructive pulmonary disease (COPD) is a chronic lung disease that has significant extrapulmonary effects that may impact the severity of symptoms in individual patients. COPD is a highly prevalent disease worldwide. The prevalence is variable between countries, but overall there is a prevalence rate of around 10% in individuals aged 40 and above (1). In developed countries, COPD is responsible for approximately 4% of all deaths and is the only major condition for which the burden of disease continues to increase, currently being 5th overall in underlying cause of death and 3rd for burden of disease (2).

Anxiety and depression are well-recognized major comorbidities in COPD (3), and consequently there has been a surge in clinical and research interest in reducing the negative impact of these important comorbidities in patients with COPD (4). This review provides an overview of the pathophysiology associated with anxiety and depression in COPD patients, the prevalence and impact of these comorbid conditions, and the strategies for their diagnosis and treatment. Areas of need for future research are also highlighted.

Prevalence of anxiety and depression as comorbidities in COPD

Like other major chronic diseases, COPD has a significant

impact on psychological well-being of people affected. Patients with COPD have a higher prevalence of depression and anxiety than the general population (5) and COPD patients have relative risk of 1.69 of developing depression (6). The rates of both anxiety and depression may even be more prevalent among COPD sufferers compared with other chronic diseases (7).

The reported prevalences of each condition are quite varied, depending on the population surveyed and the tools used to assess depression and anxiety. For patients with stable COPD in primary care settings or respiratory clinics, the prevalence of depression varies widely from 10% to 57% (5,8), and for anxiety, prevalence ranges from 7% to 50% (5,9).

Risk factors for increased rates of depression include living alone (10) and gender. Females have a higher rate of both anxiety and depression (11-13), and rates of depression are more strongly correlated with severity of dyspnoea as compared with males (12). Increasing severity of COPD is associated with higher rates of depression and anxiety (14,15); for example, in patients requiring long-term oxygen, 57% were found to have depressive symptoms and 18% had depression classified as severe (16). End-stage COPD patients undergoing palliative care also have high rates of anxiety and depression (7).

Other important risk factors are patients that have been hospitalized for an exacerbation of COPD or recovering from an exacerbation (17,18), severity of respiratory symptoms especially dyspnoea (19), living alone, and severe impairment of physical functioning (9,10).

Pathophysiological mechanisms for anxiety and depression in COPD

The aetiology of the association between depression and COPD is not fully understood; however the relationship is complex and interactive. The most important risk factor for COPD is smoking. Smoking and depression have a bidirectional interaction. Depressed individuals are more likely to smoke (20), display higher risk to commence smoking (21,22), and find smoking cessation more difficult (20,23). Conversely, smokers are more likely to be depressed (24), which could be caused by activation of nicotinic acetylcholine receptors (25), or direct inflammatory effects of smoking (26).

Although smoking could have some part to play as a causative factor for depression, depression is still more prevalent among COPD patients than smokers without COPD (13). A possible mechanism could be related with 'overspill' of local lung inflammation in the circulation (26,27). It has been speculated that systemic inflammation may play a role in the presence of depression (28). Although there are difficulties in quantification of inflammatory markers in the 'overspill' theory (26), sTNFR-1 has shown a strong association with rates of depression in COPD patients (27), while TNF-α has shown conflicting results (28,29). It is not clear if the presence of systemic inflammation has a causative association with depression or that it is a marker a specific COPD phenotype; such as frequent exacerbators (27).

Hypoxia is an additional factor that may play a role in the development of depression in COPD. Low arterial oxygen saturation has been shown to be associated with periventricular white matter lesions (30), which are present in patients with depression (31). However, the significance of these findings is contentious since the localization of subcortical hyperintensity in depressed patients has been found to be variable due different imaging technologies, lesion definition and measurement techniques (31,32).

Although smoking, inflammation and hypoxia have potential impact on the prevalence of depression in COPD, the strongest predictors of depression among patients with COPD are their severity of symptoms and reported quality of life (13). Functional limitations have been similarly shown to mediate depression in other disorders such as arthritis and heart failure (33). The amount of perceived instrumental support (the need of assistance for activities of daily living) among COPD patients has also been shown to be correlated with depression (34).

Several theories have been proposed to explain the overlap of anxiety and panic attack symptoms with COPD (35). Hyperventilation is defined as the exaggerated breathing in excess of metabolic need, causing lowering pCO_2 and causing respiratory alkalosis (36,37). This pattern of breathing can cause dyspnoea in healthy individuals and consequently panic attacks in those predisposed patients (37).

In panic disorder patients it is possible to evoke symptoms of dyspnoea and chest pain when infusing lactate or inhaling excessive CO_2 (37). These findings are the basis of the carbon dioxide hyperventilation model (35). Areas of the brain with intrinsic CO_2/H^+-sensitive neurons such as the ventrolateral surface of the medulla and locus coeruleus are involved in ventilation, but also play role in panic behaviours. The activation of these areas may concomitantly activate a defensive behavior and precipitate a panic attack (37).

Another important theory is the cognitive behavior

model which is based on the principle that normal bodily sensations are misinterpreted by patients with panic disorder and can consequently cause a panic attack (35). This misinterpretation may be associated with a behavioural sensitization event (trauma), since 20-30% of healthy panic disorder patients had a near-drowning or suffocating past experience (37). COPD patients are at greater risk of a traumatic event caused by an exacerbation, which may lead to an increased risk of developing panic disorders.

The pathophysiology of anxiety and depression among COPD patient is complex and poorly understood. Patients with depression and anxiety are at higher risk of developing COPD due to smoking. Likewise the physical, emotional and social impact of COPD is correlated with development depression and anxiety. This complex interaction between COPD and mental health diseases may cause a self-perpetuating cycle that has a severe impact upon a patient's well-being.

Impact of depression and anxiety on COPD

Depression and anxiety have considerable impact on patients with COPD, in terms of associations with mortality, exacerbations and quality of life.

Effect on mortality

Among COPD patients, depressive symptoms are associated with increased mortality among hospitalized (18,38) and community patients (15,39-41). Some studies of COPD patients have shown an association of anxiety with increased mortality (18,38,42), whereas others have failed to show any association (41). A recent meta-analysis demonstrated that in COPD patients, comorbid depression and anxiety were associated with increased risk of mortality with relative risks of 2.29 and 1.27 respectively (6).

Importantly, a prospective study by Divo and colleagues, from the BODE cohort, has demonstrated that anxiety among female COPD patients was associated with a significant increase in mortality, with a hazard ratio of 13.76 which was more than the risk conferred by coronary heart disease, heart failure, or lung cancer (43). The potential causes of this increased mortality with anxiety are probably multifactorial. One factor is treatment compliance; for example, patients with depression are more likely to not complete rehabilitation (44,45). A meta-analysis has showed that patients with depression and anxiety symptoms are 3 times more likely to be non-adherent to their prescribed medications (46). Alternatively, anxiety may be secondary to the severity of the underlying COPD, and could therefore be a clinical marker of disease severity and risk of death.

Effect on exacerbations

Among COPD patients, exacerbations contribute significantly to morbidity and mortality (47). A systematic review of 20 studies has shown that depression and anxiety increases the risk of hospitalization for COPD patients (48). A meta-analysis by Laurin *et al.* showed that the relative risk of in-hospital treated COPD exacerbation was 1.12 for depression and 1.18 for comorbid depression and anxiety (49). Anxiety and depression symptoms were also associated with increased length of stay in hospital for COPD exacerbations (18,50,51).

There are multiple possible links between depression and anxiety, and increased rates of COPD exacerbation. The impact of symptoms of depression and anxiety could place patients at risk due to non-adherence with treatment (46,52), and suboptimal success with smoking cessation (18,49). Depression could have direct effects by impairing the immune system and consequently predisposing to infections (53) leading to increased frequency of exacerbations. Worsened perception of dyspnoea may lead patient to seek medical attention unnecessarily and increase hospital admissions; patients with anxiety and depression during admission have worse dyspnoea scores despite having less severe physiological parameters (e.g., pH, partial pressure of oxygen and carbon dioxide) (54). The meta-analysis by Laurin *et al.* has shown that patients with anxiety were at greater risk for exacerbations that required treatment in the community, whereas those with depression were at higher risk for exacerbations requiring treatment in hospital (49). This discrepancy could be explained by "early intervention" among anxious patients that could prevent the need for treatment in hospital (49).

Effect on quality of life

The detrimental impact of COPD on quality of life is well-documented (3). Depression and anxiety symptoms also have significant impact on quality of life and functional status in many chronic diseases (55,56). In general, patients with depression and anxiety perceive their health as poorer than the average population (57). Specifically for COPD, the impact of quality of life and functional status is also evident in several studies, independent of the severity of

COPD or related comorbidities (14,56,58-62). A meta-analysis showed that the presence of depression and anxiety among COPD patients was one the strongest correlations with self-reported health status (63). Comorbid depressive symptoms in patients with COPD are associated with persistent smoking, increased symptom burden, poorer physical and social functioning (18), and difficulty in performing daily activities (64). Low self-confidence or self-efficacy is also common, which may lead to worsened ability to cope with chronic disease (49,56).

Depression and anxiety symptoms are associated with increased perception of dyspnoea (54,65,66). The presence of psychological symptoms (mainly depression and to lesser extent anxiety) has an effect on vital exhaustion, defined as a state characterized by fatigue and lack of energy, worsening irritability and feelings of demoralization (67). Fatigue and especially dyspnoea are independently negatively associated with poor health status (63,68).

The impact of depression and anxiety symptoms are not limited to an individual's lung disease. The presence can influence a person's end of life decisions (69) or may have negative impact upon partners and their respective relationships (70).

Diagnosis and screening of depression and anxiety

The gold standard for the diagnosis of depression or anxiety is based in the criteria listed in the DSM-IV and achieved through structured interviews performed by a psychiatrist or a clinical psychologist. As there is a strong positive relationship between self-reported severe symptoms and the existence of a mental disorder (71,72), screening instruments have also been developed, which are less costly, faster and easier to administer. These instruments can also monitor clinical outcomes of mental health treatments (73,74).

Several screening tools have been validated for use in COPD patients. The Geriatric Depression Scale and its 15-item short form (GDS-15) are validated as depression tools (75), and the Hospital Anxiety and Depression Scale (HADS) and the Geriatric Anxiety Inventory (GAI) have been validated for anxiety in COPD patients (76). Anxiety Inventory for Respiratory (AIR) Disease and Brief Assessment Schedule Depression Cards (BASDEC) are two other scales that have been developed exclusively for COPD (9,77).

There are concerns regarding the use of screening instruments due to the risk of false positives caused by the overlap of symptoms (78), and the uncertainty regarding impact on routine practice (79,80). The Global Initiative for Chronic Obstructive Lung Disease guidelines recommend that new COPD patients should have a detailed medical history including for depression and anxiety (3). However, to date, there is no consensus on the most appropriate screening approach for anxiety and depression (81).

Treatment approaches for anxiety and depression in patients with COPD

Depression and anxiety, when coexisting with COPD, significantly impact quality of life and functional outcomes. In acknowledgement of the biopsychosocial impact of chronic ill health, the World Health Organization has stated that patients with chronic diseases such as COPD should receive integrated care programs which are centered on the patient rather than just the disease (82). Fortunately, interventions targeting these psychological comorbidities are well-established for the general population (83). However psychological care guidelines are less well developed for the specific COPD patient population (84). Where psychological treatments have been used in COPD, these have typically been based on guidelines already in use for depression and anxiety in the wider population (85). Treatments can be divided into psychological [relaxation, cognitive behavioural therapy (CBT), self-management] and pharmacological interventions. Pulmonary rehabilitation, a specific treatment for COPD, also has beneficial effects on anxiety and depression.

Psychological therapies

For patients with a chronic health condition who are also experiencing clinical or sub-threshold depression, the UK's National Institute for Health and Care Excellence (NICE) recommends use of low to high intensity psychosocial interventions depending on the severity of mood symptoms (85). Low intensity interventions may include individual or self-help programs, or online CBT, while high intensity interventions are typically individual or group CBT sessions. These recommendations are based on moderate quality randomized controlled trials and the experience and opinion of the Guideline Development Group (85). While the NICE guideline targets general chronic health presentations, good quality studies are somewhat lacking in COPD-specific populations. Existing studies show mixed results that are difficult to compare, because of factors such as small sample size, varied populations, lack of data on

disease severity and differences in the screening tools used to assess these patients. A recent meta-analysis has described the benefits of the most common psychological interventions—relaxation therapy, CBT and self- management education programs (83).

Relaxation therapy

The aim of relaxation therapy is to promote psychological change through techniques that create a relaxed state. Techniques commonly used range from breathing exercises, hypnoses, meditation, body positioning, sequential muscle relaxation, mild forms of exercise and visualization techniques (86). These methods are used separately or as a element of other psychological treatments or pulmonary rehabilitation (4).

The effectiveness of relaxation-based therapies for COPD was evaluated in a meta-analysis by Devine *et al.*, which showed significant improvements in symptoms of dyspnea and anxiety (87). For patients undergoing a pulmonary rehabilitation program, progressive relaxation techniques administered by tape-recorded classes showed a non-significant improvement in depression and, to a lesser extent, anxiety symptoms at the time of the end of the pulmonary rehabilitation program (88). There have been several smaller studies that have investigated other types of relaxation approaches. One small study using tai chi demonstrated a non-significant improvement of depression, dyspnoea and physical capacity as measured by six minute walk test results (89). A study examining yoga as the intervention showed a significant improvement in six minute walk results and functional performance, non-significant improvement in dyspnoea score and quality of life, but no change in anxiety or depression scores (90). In these types of studies, it is often difficult to determine whether the benefit is due to the physical activity or the relaxation components of the treatment.

Loosely related to relaxation interventions, singing classes have also been used as an intervention in COPD patients. The underlying theory is that singing lessons might improve patient quality of life and/or functional status by offering techniques that address both the sensory component of dyspnoea (e.g., control of respiratory pattern to reduce hyperinflation) and the affective component (e.g., anxiety and low mood around perceived breathlessness) (91). A moderate-sized study employing singing classes showed improvement in anxiety levels and the physical component of a quality of life questionnaire (92). In a further study by the same researchers, the improvements remained after controlling for the incidental beneficial effects of social interaction amongst the participants (93). In regards to these less traditional interventions, there is still a lack of clarity about their applicability, their long-term effectiveness, the active component (physical or psychological), and how they may be incorporated into standard care.

Cognitive behavioural therapy (CBT)

CBT is a type of psychotherapy used in the management of a range of psychiatric disorders. It is based on an information-processing model in which emotional symptoms are thought to be driven by negatively-biased evaluations of the world, the future, or the self (including bodily sensations) (94). Often performed in collaboration between the therapist and the patient, CBT utilizes a number of strategies to correct those biased evaluations and provide skills aimed at controlling their symptoms and consequently improving the management of their illness (4).

The use of CBT has gained traction because of its effectiveness in achieving symptomatic relief for patients with chronic illnesses (56,95). There have been numerous studies of varying quality and sample size that have shown promising results (96-101) (*Table 1*). The studies showed small to moderate improvements in anxiety and depression scores and quality of life; however direct comparison is hampered by the fact that interventions varied in regard to number of sessions, duration of each session and delivery format (group or face to face). The fact that positive impact was demonstrated in most studies, even those with shorter interventions, holds promise for future applicability.

Cost-effectiveness is undoubtedly an important issue, particularly given tightening health budgets, and increasing service imperatives to reduce health care spending. One study has shown that face-to-face CBT is effective and also may be cost neutral when implemented in COPD patients (95). If other less expensive approaches are interchangeable to face-to-face they may be more economically attractive. The use of telephone-based interventions for depression has shown to be just as effective as face-to-face (102-104), and such an approach has also been shown to be beneficial for patients with anxiety and depression associated with other chronic diseases (105,106). A novel alternative approach is the use of an Internet-based intervention, which has been shown to be as effective as face-to-face interventions for depression and anxiety (107-109). CBT-based therapies, particularly tightly manualised therapies for sub-clinical anxiety or depression, may not require a fully trained psychologist for its administration, adding to overall cost effectiveness. A nurse-

Table 1 Major randomized control trials involving cognitive behaviour therapy and COPD for anxiety and/or depression

First author, year	Study design	Patients	Measures	Treatment and comparison	Results
Livermore *et al.*, 2010 (100)	RCT Outpatients Attended pulmonary rehabilitation program Panic attacks and panic disorder were diagnosed with the ADIS-IV	41 patients; 21 CBT, 20 control CBT: Age 73.2±6.4 43% male Control: Age 73.5±8.1 45% male	Primary: Rates of panic attack and anxiety symptoms Panic attacks and panic disorder were diagnosed with the ADIS-IV Secondary: HADS IPBQ SGRQ COPD-related admissions	Intervention: 4 individualized 1 hour sessions and manual (with strategies effective for the prevention and treatment of panic disorder in younger adults) Follow-up: post intervention, 6, 12 and 18 months	ADIS-IV there were significant differences post-intervention and at the 6-, 12- and 18-month No panic attacks in intervention group while no CBT had 35% post intervention tie and 60% at 18 months Significant difference in HADS score at 6-, 12- and 18-month follow-up Significant positive effect on IPBQ No differences in HADS depression scale, SGRQ Significant decrease in hospital admission rate between 6 and 12 months
Hynninen *et al.*, 2010 (97)	RCT Clinically significant anxiety and depression Outpatients Scores >15 BAI and/or >13 on the BDI-II	41 patients; 25 CBT and 26 control 17 participants (33.3%) fulfilled the diagnostic criteria for a mood disorder CBT group: 56% male Age 59.3±7.6 Control group: 42% male Age 62.6±9.9	Primary: BAI BDI-II Secondary: SGRQ PSQI Actigraphy CSQ	Intervention CBT: 7 sessions of 2 hours of group CBT psychology students. Telephone session at 1 and 3 months after Control: telephone contact every 2 weeks for 7 weeks. Call lasted 5-10 minutes Follow-up 8 months	Significant improvement of BAI and BDI-II after treatment and on follow-up Control had no improvement Women had more anxiety and depression, responded more however had more significant anxiety and depression at the end of treatment Treatment was intensive although response was rapid
Kunik *et al.*, 2008 (99)	RCT Outpatients Stable COPD Scores ≥16 BAI and/or >14 on the BDI-II No smoker , low MMSE (<23) or psychiatric disorder	138 patients; 118 to CBT, 120 to control 95% males Education group: 95.8% male Age 66.5±10.4 CBT group 96.6% male Age 66.5±10.1 62.2% had a DSM-IV diagnosis of depression or anxiety	Primary: QoL CRQ SF-36 Secondary: BAI BDI-II 6MWD Use of health services	Intervention: 8× 1 h CBT sessions, group sessions Control: 8× 1 h COPD education sessions Both by same therapist Follow-up: weeks 4 and 8 and months 4, 8 and 12	Both treatments significantly improved QoL with trend favoring CBT group Improvement of SF-36, anxiety and depression (P<0.005) over 8 weeks for both groups No change of 6MWD for either group Follow-up at 8 and 52 weeks showed no change in improvement obtained at end of therapies

Table 1 (*continued*)

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First author, year	Study design	Patients	Measures	Treatment and comparison	Results
de Godoy *et al.*, 2003 (101)	Single blinded RCT COPD attending a pulmonary rehabilitation program	32 patients; 14 to CBT, 16 control CBT: 85% male Age 62.1±14.9 Control: 62.5% male Age 58.8±11.8	BDI BAI 6MWD	Intervention: 12 sessions of psychological sessions: Cognitive therapy and logo therapy techniques Both had 12 weeks of rehab with: 24 sessions of physical exercise, 24 sessions of physiotherapy, 3 educational sessions	Significant improvement in BAI, BDI and 6MWD 6MWD improved for both groups, higher improvement in group treated with psychotherapy, although the improvement was not directly related with improvement of anxiety and depression
Kunik *et al.*, 2001 (98)	Single blind RCT Outpatients, from veteran hospital Stable COPD	50 patients; 21 CBT and 29 education group CBT and education: Age 71.3±5.9 83.1% male	SF-36 GDS BAI 6MWD FEV_1	Treatment: same education session lasting 2 hours and 1× 2 h session of group CBT Control and treatment: 1× 2 hour education session focusing on COPD process, etiology and treatment options Weekly calls for 6 weeks for both	Statistical Improvement in BAI and GDS and one measure of SF-36 (mental health question) Non statistical improvement of 6MWD
Emery *et al.*, 1998 (96)	RCT Three groups; Exercise, education and stress management (EXESM), Education and stress management (ESM) and waiting list (WL) Outpatients 79 community-based out-patients	79 patients; 30 EXESM, 24 ESM and 25 WL EXESM: Age 65.4±6.4 50% male ESM: Age 67.4±5.9 41.6% male WL: Age 67.4±7.1 48% male	Anxiety and depression: CES-D The Bradburn Affect-Balance Scale STAI SCL-90-R Health-related quality of life: MHLC SIP Cognitive test battery Pulmonary rehabilitation health knowledge test Bicycle ergometry testing	EXESM: 10 weeks: 37 exercise sessions, 16 education sessions, 10× 1 hour stress management sessions based on CBT and delivered by clinical psychologist ESM: 16 education sessions, 10× 1 hour stress management sessions based on CBT and delivered by clinical psychologist WL: Awaiting to be in study. 25 patients Follow up at 10 weeks	VO_2 max = maximal oxygen consumption during bicycle test – improved only with exercise program. However it was not a predictor of any other outcome. Depression improved with exercise and waiting. No improvement with education and psychology Anxiety reduced more with exercise that without. SIP improved with EXESM and WL Verbal processing improved only with EXESM EXESM and ESM improved health knowledge

BAI, Beck Anxiety Inventory; BDI-II, Depression Inventory-II; SGRQ, St George's Respiratory Questonaire; PSQI, Pittsburgh Sleep Quality Index; CSQ, The Client Satisfaction Questionnaire; Disease-specific and generic quality of life (QoL), CRQ, Chronic Respiratory Questionnaire; 6MWD, 6-minute walk distance; CES-D, The Center for Epidemiological Studies-Depression Inventory; STAI, The State-Trait Anxiety Inventory; SCL-90-R, The Hopkins Symptom Checklist; MHLC, The Multidimensional Health Locus of Control; SIP, The Sickness Impact Profile; IPBQ, The Interpretation of Breathing Problems Questionnaire; ADIS-IV, Anxiety Disorder Interview Schedule. Disease-specific and generic quality of life (QoL), Medical Outcomes Survey Short Form-36 (SF-36).

administered minimal psychological intervention (MPI), based on the principles of CBT and self-management, was used in one study of COPD patients and showed promising results (110).

Not all aspects of CBT therapy may be necessary to produce a therapeutic effect. Purely behavioural interventions can be as effective as CBT for patients with depression (111). They are simpler to administer and theoretically could be used for patients with COPD.

Self-management strategies

Self-management programs aim to improve patient care by providing resources and guiding health behaviour change in ways that empower the individual. This empowerment is thought to increase their ability to carry out medical regimens designed to control their chronic disease, improve well-being and decrease exacerbations (112-114). Many self-management programs incorporate aspects of CBT.

The effects of self-management programs for patients with chronic health conditions are still unclear, and the results have been modest when compared to more specific psychological interventions (83). Jonker *et al.* found improvement in self-efficacy in older people, but no reduction in health care utilization or improvement in quality of life (112). In cardiac patients one study reported a moderate effect of self-management on functional outcomes and depressive symptoms after an acute coronary syndrome (115). For COPD patients, although a review by Kaptein *et al.* reported favourable outcomes for self-management on frequency of hospitalisation, greater exercise tolerance and increased quality of life (116), in the meta-analysis of 29 RCTs by Coventry *et al.*, there was no overall benefit for self-management education alone for anxiety and depression in COPD (83).

A large multicenter randomized trial in COPD patients showed that a self-management intervention reduced exacerbation rates (114). Similarly, a Cochrane review by Effing *et al.* (113) showed a significant and clinically relevant reduction in the number of patients with one or more hospital admissions and a small but significant reduction of dyspnoea scores. Results were inconclusive for anxiety and depression symptoms, doctor and nurse visits, the use of courses of oral corticosteroids and antibiotics, and the use of rescue medication. No effects were seen for ER visits, lung function, exercise capacity, and days lost from work (113). Interestingly, conflicting results for quality of life questionnaires were seen, as a positive trend was seen for the St. Georges Respiratory Questionnaire (SGRQ), but not for SF-36 (113). This last result highlights the need for precision and clarity in the description of the construct being measured (e.g., quality of life) and consistency in the selection of measures. The wide range of measures used across the papers surveyed herein reveals the difficulty in both assessing the effectiveness of interventions within a study, and comparing findings across studies reported in the literature.

Finally, health mentoring is a self-management intervention that uses cognitive behavioural techniques to provide skills to improve self-efficacy and disease management, and to change unhealthy behaviours (117). Nursing-based mentoring has shown conflicting results with one study showing benefit in quality of life for patients with COPD (118), while other studies have failed to show any positive effect on quality of life (119,120) or anxiety and depression symptoms (119). A meta-analysis has shown case management was the least effective intervention for reducing anxiety and depression when compared to CBT, relaxation or self-management intervention (83).

Pharmacotherapy

Pharmacotherapy is a mainstream treatment for anxiety and depression. Although there is some controversy regarding effectiveness, meta-analyses have shown the overall benefit of pharmacotherapy in the treatment of anxiety and depression (121). In standard clinical practice, antidepressants are the main medication used for depression and anxiety. Other less common agents used are benzodiazepines, antipsychotics, anticonvulsants and azapirones (4).

Antidepressants work mainly by increasing synaptic monoamines, dopamine, serotonin and/or noradrenaline. They have similar effectiveness but mainly differ based on type and severity of side effects. The main categories are: selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenaline reuptake inhibitors, tetracyclic antidepressants, tetracyclic analogues of mianserin [sometimes called noradrenergic and specific serotonergic antidepressants (NaSSA)], tricyclic antidepressants (TCAs), reversible inhibitors of monoamine oxidase A (RIMAs), monoamine oxidase inhibitors (MAOIs) and melatonergic antidepressants [summarised in (122)]. Antidepressants are a moderately effective treatment for depression in healthy individuals, more so in cases of greater severity and in melancholia, but there is less certainty in physically ill patients. Among this population with subthreshold

symptoms of depression (symptoms that are below the DSM-IV criteria for major depression) or mild to moderate depression, NICE guidelines advice that antidepressants should not be routinely prescribed (72).

A recent Cochrane review of antidepressants (mostly SSRI and TCA), for the treatment of depression or depressive symptoms among physically ill patients, demonstrated a significant improvement among patients with depression or milder depressive disorder, and a positive trend for depressive symptoms and other depressive disorders (123). This Cochrane review also observed that there was greater long-term improvement for SSRIs compared to TCAs. A study assessing the effects of the SSRI, fluoxetine, in hospitalized patients with depression showed a positive trend towards improvement of depression symptoms specially for those patients that were more severely ill (124).

In contrast to the wider general population or physically ill, at present, the data for efficacy of pharmacotherapy for anxiety and depression are limited for COPD. The main studies have been of SSRIs and TCAs. SSRIs are the first line pharmacotherapy treatment for depression and anxiety (125). For depression, small studies in COPD have shown mild improvements. Two studies of COPD patients using paroxetine showed variably significant improvement in quality of life questionnaires (126,127), and improvement of anxiety and depression scores and physical capacity after 3 months (127) (*Table 2*). A single-blinded open trial study of 57 COPD patients, aiming to assess the acceptability of fluoxetine therapy, showed that over two-thirds of patients declined to use fluoxetine therapy, mostly related to patient biases regarding use of psychiatric medication (128) (*Table 2*).

For TCAs, a number of small studies have been conducted in COPD. A study by Borson *et al.* showed that nortriptyline was effective in reducing depressive and anxiety symptoms and in increasing physical function (131), although a crossover study of similar size failed to show any benefit when using doxepin for patients with symptoms of anxiety and depression (129). In another study using protriptyline, the majority of the patients did not complete the trial because of the anticholinergic side effects (130). TCAs are no longer first line treatment for depression or anxiety, and consequently future trials for this medication class are unlikely (132).

Regarding the treatment of anxiety in COPD patients, a Cochrane review was unable to undertake any meta-analysis due to poor quality of the studies and very small sample sizes (122). Only four studies were analyzed, with two studies using SSRIs, and the other two using a TCA and azapirones. Two studies using SSRI showed a non-significant reduction in anxiety symptoms (122,127). The studies using TCA and azapirones did not show any improvement (129,133).

As was the case for psychological treatment, the overall effectiveness of pharmacotherapy for anxiety or depression in COPD has not been rigorously tested. Studies in COPD have been small, with large heterogeneity of sampling and tools used to assess efficacy of the treatments. In addition, there is limited evidence regarding the impact of side effects of pharmacotherapy, such as dry mouth and sexual dysfunction (123). Some side effects of treatment (such as dry mouth) may compound adverse effects of medications used for COPD, notably the anticholinergic activity of long-acting muscarinic antagonists (134). In addition, there are issues regarding patient refusal to take antidepressants due to misconceptions regarding depression and addiction, stigma associated with the disease, and lack of interest and motivation (132). Clearly, much more work needs to be done to test pharmacotherapy for anxiety and depressive symptoms in COPD, and to undertake head-to-head comparisons with psychological interventions and combinations of treatments (121).

The role of pulmonary rehabilitation

Pulmonary rehabilitation is an essential component of standard care for people who are symptomatic from chronic lung diseases causing breathlessness and functional impairment, such as COPD (135,136). Large observational studies of pulmonary rehabilitation participants have reported the prevalence of anxiety symptoms to range between 25% (137) and 32% (138), and depressive symptoms to range between 17% (137) and 27% (138). The symptoms of anxiety and depression have been associated with program non-completion (137,139), increased dyspnoea, fear of exercise and reduced functional performance both at commencement and completion of pulmonary rehabilitation (140,141). Furthermore, improvement in the symptoms of depression has been associated with improvements in specific domains of health-related quality of life (142). However, it is unclear if the symptoms of anxiety and depression should be addressed prior to entry to a pulmonary rehabilitation program or during the program.

Importantly, the symptoms of anxiety and depression have been shown to improve following completion of

Table 2 Example of studies involving pharmacotherapy and COPD for anxiety and/or depression

First author, year	Study design	Population	Measures	Results
Eiser *et al.* 2005 (127)	Double blinded RCT Initial blinded for 6 weeks After all patients took un-blinded Paroxetine for 3 months Out-patients with moderate to severe, stable COPD Patients screened using HAD and depression further diagnosed by psychiatrist	28 patient were diagnosed with depression 14 patients in each group 14 females and 14 males, mean age 66	HAD BDI Psychiatrist completed MADRS SGRQ 6-minute walking test	6 weeks' treatment produced no significant differences between placebo 5 patients treated with paroxetine developed side effects and medication was changed Three months of un-blinded treatment: Significant improvement in HAD, BDI and MADRS Significant improvement in walking distances (369 to 427 m, P=0.0003) Significant improvement in St. George's Respiratory Questionnaire Total Scores (65 to 58, P=0.033)
Lacasse *et al.* 2004 (126)	Double blinded randomized control trial Treatment was paroxetine for 12 weeks Outpatients with severe COPD, oxygen dependent GDS >11/30	23 patients entered the trial. 82 refused Treatment group (12 patients, 5 males, mean age 71.2 Control group (11 patients, 5 males, mean age 69.8	CRQ SF-36 GDS Side effects Compliance	2 patients on paroxetine did not tolerate maximum dose Clinical and statistical improvement in emotional domain of CRQ Non significant improvement in GDS
Yohannes *et al.* 2001 (128)	Single-blinded (open) study. Paroxetine for 6 months Inpatients with moderate to severe COPD GMS diagnosed depression	57 (25 males and 32 females) Mean age 72 14 accepted treatment with fluoxetine	BPQ, MRADL were done as baseline MADRS	7 subjects completed the trial 4 (57%) responded to fluoxetine therapy 5 subjects withdrew because of side effects
Light *et al.* 1986 (129)	Double-blind crossover study Doxepin or placebo for 14 weeks Outpatients, at least moderately severe COPD	12 patients (all male), 6 patients for each group 3 ceased doxepin due to side effects, 9 completed trial Aged 57 to 69 (mean 61.2)	STAI BDI FEV_1, PaO_2, $PaCO_2$ 12 minute walk test	No improvement in any of the measures (anxiety and depression scores, respiratory function and physical capacity) Worse mean depression score for the treatment group Half ceased therapy due to side effects (drowsiness, blurred vision, nausea and vomiting)
Ström *et al.* 1995 (130)	Double blind randomized trial Outpatients, COPD stable with mild or moderate hypoxaemia Treatment with Protriptyline for 12 weeks	26 patients 14 patients on treatment group and 12 on placebo group Treatment group had 4 males and 10 females. Aged 57 to 75 (mean 66) Placebo group had 4 males and 8 females. Aged 52 to 66 (mean 59)	SIP MACL HAD Dyspnea score Exacerbations Arterial blood gas Respiratory function	No improvement in all measures (arterial blood gas tension, spirometry, quality of life, anxiety and depression score, dyspnea score and exacerbations) 12 of 14 patients on protripyline had side effects. 6 of 12 patients on placebo had side effects

HAD, Hospital Anxiety-Depression; BDI, Beck's Depression inventory; MADRS, Montgomery Asberg Depression Score; St. SGRQ, George's Respiratory Questionnaires; CRQ, Chronic respiratory questionnaire; GDS, Geriatric depression scale; GMS, The Geriatric Mental Status Schedule; MRADL, Manchester Respiratory Activities of Daily Living Questionnaire; BPQ, Breathing Problems Questionnaire; STAI, State-Trait Anxiety Inventory; MACL, Mood Adjective Check List; Hospital Anxiety and Depression (HAD) scale, Medical Outcomes Survey Short Form-36 (SF-36), Sickness Impact Profile (SIP) questionnaire.

comprehensive pulmonary rehabilitation (143,144). In a large randomised controlled trial, participants completing pulmonary rehabilitation were shown to significantly improve symptoms of anxiety and depression when compared to the control group of usual care (144). Studies have also shown that participants with symptoms of anxiety or depression can gain similar improvements in other program benefits arising from pulmonary rehabilitation. For instance, in an observational cross-sectional study, individuals with symptoms of anxiety and depression had similar benefits in exercise capacity and health-related quality of life following pulmonary rehabilitation as participants not experiencing these symptoms (145). Moreover, another observational study reported that participants with greater symptoms of anxiety in fact had a larger improvement from exercise training following pulmonary rehabilitation (146). Therefore, the recent guideline on pulmonary rehabilitation in adults from the British Thoracic Society states that the psychological status of participants is improved with pulmonary rehabilitation when compared with usual care, and recommends that individuals with symptoms of anxiety and depression should not be excluded from pulmonary rehabilitation (147).

Recommendations and future directions in research and practice

Full spectrum anxiety and depression are highly prevalent among patients with COPD and are associated with poorer outcomes. This seems to hold even for milder or sub-threshold levels of anxiety and depression. The first step to improve practice is to achieve earlier and more accurate diagnosis of these psychological comorbidities in COPD. This is important since these conditions are underdiagnosed and consequently undertreated (8,58). Self-reported screening instruments are useful as an initial approach; however validated tools should then be utilized to minimize false positives and standardize care. When and in whom screening should be done is still not clear for patients with COPD. It is also not clear if it should be carried out with all COPD patients or just to those at higher risk of these comorbidities. After the psychological distress screening scale has been performed, high-scoring patients should be referred to a mental health specialist to facilitate access to comprehensive, gold-standard diagnostic assessment (85).

Due to the impact of associated depressive and anxiety disorders and symptoms on COPD patients, determining the best treatment approach is essential. Unfortunately, as highlighted in this review and by others, there is currently a relative scarcity of strong evidence of benefit for any specific pharmacological or non-pharmacological treatment for anxiety and depression in COPD (4). Furthermore, at this point of time, guidelines are based on treatment of depression and anxiety for the general population (3).

Due to the bidirectional nature of the association of COPD with depression and anxiety, an integrated approach that enhances the benefits between mental and physical health would be the most effective. There is extensive evidence of the benefits of pulmonary rehabilitation for patients with COPD and it has shown to significantly reduce symptoms of both anxiety and depression in COPD patients, possibly through improved physical capacity (148). Adding a depression or anxiety targeted treatment to the pulmonary rehabilitation program may have additive therapeutic benefits. This synergistic effect has been alluded to in a study where marked improvement in depression symptoms was shown when brief inpatient pulmonary rehabilitation plus antidepressants were used with COPD patients with major depression (149). Similarly, another study showed a significant improvement in anxiety and depression with improvement of physical capacity, when CBT was provided within a pulmonary rehabilitation program (101).

Future studies should aim to fill the current gaps in knowledge about treatment of psychological symptoms in COPD. First there are no large studies that have definitively assessed the true benefits of psychological, pharmacological or combined treatment modalities in the COPD population. Future studies should also focus on determining the best treatment for specific COPD groups e.g., based on gender, severity of COPD and frequency of exacerbations. There is also uncertainty regarding the cost-effectiveness of targeted treatment of anxiety and depression, and feasibility of restructuring health-care delivery to incorporate care for mood and anxiety disorders as an integral part of high quality, comprehensive chronic disease management of patients with COPD.

Summary

This review has provided an overview of the pathophysiology, prevalence and impact of anxiety and depression in patients with COPD, and has discussed diagnosis and treatment options for these important psychological comorbidities. In COPD patients, the presence of symptoms of anxiety and depression are common and have significant impacts that, adversely affect mortality rate, exacerbation rates,

hospital length of stay, quality of life and functional status. Anxiety and depression are underdiagnosed in patients with COPD, and consequently undertreated. Studies examining specific pharmacological and non-pharmacological treatment of these conditions are limited and generally are comprised of small studies of varying quality. Given the current state of knowledge, many further areas of research are needed in the field of COPD chronic disease management, including in whom to screen for clinically important anxiety and depression, and the most effective and cost-effective treatment approaches for these conditions in COPD patients. A much greater awareness of the clinical importance of mental health comorbidities in COPD is urgently needed.

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