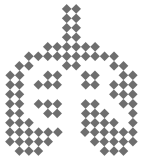
Eur Respir J 2008; 31: 667–677
DOI: 10.1183/09031936.00125707



SERIES "COMPREHENSIVE MANAGEMENT OF END-STAGE COPD"
Edited by N. Ambrosino and R. Goldstein
Number 3 in this Series

Anxiety and depression in end-stage COPD

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ABSTRACT: Although feelings of anxiety and depression are common in patients with chronic obstructive pulmonary disease (COPD), estimates of their prevalence vary considerably. This probably reflects the variety of scales and methods used to measure such symptoms. Regardless of whether anxiety and depression are considered separately or as a single construct, their impact on COPD patients is important.

A heightened experience of dyspnoea is likely to be a contributing factor to anxiety. Feelings of depression may be precipitated by the loss and grief associated with the disability of COPD. Smoking has been associated with nicotine addiction, and the factors that contribute to smoking may also predispose to anxiety and depressive disorders.

Randomised controlled trials indicate that exercise training and carefully selected pharmacological therapy are often effective in ameliorating anxiety and depression. Most medical illnesses are influenced by the psychological responses and coping mechanisms that patients use. However, anxiety and depression are associated with dyspnoea, fatigue and altered sleep, all of which also occur in COPD.

An understanding of the psychological history and coping mechanisms of patients and the role of anxiety and depressive reactions to illness may enable clinicians to reduce these symptoms and improve quality of life among patients with chronic obstructive pulmonary disease.

KEYWORDS: Anxiety, chronic obstructive pulmonary disease, depression

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Received:
September 24 2007
Accepted after revision:
October 05 2007

STATEMENT OF INTEREST
None declared.

Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction that is not fully reversible [1]. In addition to the primary pulmonary pathology, the impact of secondary skeletal muscle dysfunction on exercise capacity and survival is well established [2, 3]. Psychological impairments, ranging from feelings of depression and anxiety to full diagnostic mental disorders, although prevalent in this population, have received less interest. As COPD is incurable, therapeutic interventions aim to optimise function and slow disease progression [4]. Attention has focused predominantly on the effectiveness of strategies such as smoking cessation [5], long-term oxygen therapy (LTOT) [6, 7], influenza vaccines [8], respiratory-specific pharmacological management [9], surgical options [10], conditioning of the peripheral muscles with graduated exercise training [11] and chronic disease self-management strategies [12].

Despite the prevalence of depression and anxiety and their impact on the morbidity associated with COPD, these psychological consequences of the disease are rarely addressed, at least in the respiratory medicine community. The purpose of the present review is to raise awareness among pulmonologists, general practitioners and allied health professionals to the secondary psychological impairment associated with COPD. Although anxiety and depression often coexist, they represent separate constructs [13]. Broader reviews of the psychological characteristics of patients with COPD are available [14].

ANXIETY

Classification and diagnostic criteria

Anxiety is defined as an apprehensive anticipation of danger or stressful situations associated with an excessive feeling of dysphoria or somatic symptoms of tension [15]. It may be characterised by restlessness, fatigue, irritability, rapid speech,

Previous articles in this series: No. 1: Viegi G, Pistelli F. Sherrill DL, Maio S, Baldacci S, Carrozzi L. Definition, epidemiology and natural history of COPD. *Eur Respir J* 2007; 30: 993–1013. **No. 2:** Fabbri LM, Luppi F, Beghé B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J* 2008; 31: 204–212.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

poor concentration, sleep distrubance and physiological changes, such as tachycardia, palpitations, sweating and dyspnoea [16, 17]. Some of the specific anxiety-related disorders include generalised anxiety disorder, panic attacks and panic disorder. According to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM) version IV [18], generalised anxiety disorder is characterised by excessive anxiety and worry, occurring more days than not, for $\geqslant$6 months, about a number of events or activities. Individuals find it difficult to control their worry, causing impaired function in social, occupational or other important areas of daily life [18]. Panic attacks have been described as intense episodes of acute anxiety that are associated with certain physical symptoms, such as dyspnoea and cognitive fears [19]. Individuals with panic disorder experience recurrent or unexpected panic attacks that are accompanied by persistent fears or worries about such attacks and their consequences [19].

Prevalence in COPD

The prevalence of anxiety in COPD is generally considered to be high. Reviews of studies that have examined feelings of anxiety in COPD patients report prevalence ranging 2–96% [14, 20, 21]. The prevalence of generalised anxiety disorder ranges 10–33% [14, 22], and the prevalence of panic attacks or panic disorder ranges 8–67% [14]. The considerable disparity in these estimates pertains to methodological discrepancies, including variations in sample size and proportion of nonparticipants, and between-study differences in assessment instruments and the threshold standards used to identify the presence of anxiety-related symptoms. Furthermore, determining the prevalence of anxiety in a COPD population is particularly difficult due to the overlap between symptoms of the disease and symptoms of anxiety [21]. Questionnaires designed to screen for anxiety that include a large number of somatic complaints, such as breathlessness and fatigue, are likely to overestimate the prevalence of anxiety in COPD, since such symptoms may also be associated with the primary respiratory impairment. Notwithstanding these considerations, greater levels of anxiety have been reported in patients with COPD compared with those with heart disease and cancer [23].

Risk factors

Few studies have investigated the relationships between the magnitude of anxiety-related symptoms and demographic or anthropometric variables in the COPD population. Greater levels of anxiety in COPD patients have been associated with poor satisfaction with marital relationships [24], and are more common in females than males and in current smokers than nonsmokers [25]. Furthermore, COPD patients with anxiety are often also depressed, with the magnitude of depression-related symptoms estimated to account for 66% of the variance in the measurement of anxiety-related symptoms [26]. In male COPD patients, low levels of perceived self-efficacy in symptom management and poorly adapted coping strategies and social support have been associated with higher levels of anxiety [27]. It is unclear whether the prevalence or magnitude of anxiety-related symptoms differ according to the severity of airflow obstruction, with some [25, 28–30], but not all [31], studies reporting no relationship between these measures. In patients with moderate-to-severe COPD, the prevalence of anxiety does not appear to be related to the level of education, age, use of LTOT or the presence of diabetes or a cardiovascular comorbid condition [25].

Mechanisms

Common mechanisms for explaining the high association of anxiety with COPD include factors related to smoking and dyspnoea. Tobacco smoking is widely acknowledged as the single most important environmental risk factor for the development of COPD [1], and high levels of anxiety have been identified as a risk factor for adolescents starting to smoke [32]. In addition, individuals with a history of an anxiety-related disorder also experience more symptoms of nicotine withdrawal on cessation of smoking [33]. Taken together, it is likely that a proportion of patients who develop COPD as a consequence of smoking showed higher levels of anxiety than the general population prior to developing the disease. Moreover, these individuals may have a greater tendency to addiction, since nicotine withdrawal is associated with greater symptoms of anxiety.

Dyspnoea is the most common and disabling symptom experienced by COPD patients [1]. Although variable in its intensity both between and within individuals, dyspnoea increases during acute exacerbations of the disease [34]. Individuals with COPD describe such episodes of heightened and intractable dyspnoea as being inextricably associated with anxious feelings [35]. The relationship between dyspnoea and anxiety explains, at least in part, the high proportion of COPD patients describing anxiety as a marker of disease exacerbation [34]. Furthermore, feelings of anger or frustration are frequently identified as a potent trigger for anxiety, which, in turn, heightens the sensation of dyspnoea [35]. Therefore, it appears that complex interrelationships between dyspnoea and anxiety contribute to the increased prevalence of anxiety-related disorders in COPD. Although pathophysiological mechanisms, such as chemoreceptor hypersensitivity to carbon dioxide, have also been proposed to link panic attacks with a heightened experience of dyspnoea in a subgroup of COPD patients [19, 36], it is important to note that the magnitude of dyspnoea at rest or on exertion does not correlate with the magnitude of anxiety-related symptoms [37]. Furthermore, it has not been convincingly demonstrated that the magnitude of decrease in dyspnoea with pharmacological therapy or exercise training is associated with the magnitude of reduction in anxiety-related symptoms. Therefore, although dyspnoea and anxiety are linked in COPD, several other factors contribute to this relationship.

Clinical features and impact

Symptoms of anxiety in COPD have been demonstrated to impact importantly on disease-specific health-related quality of life and hospitalisation rates. Specifically, the magnitude of anxiety-related symptoms has been associated with the total score [28, 37], as well as the activity and impact subscores, of the St George's Respiratory Questionnaire [25] and the dyspnoea, emotional function and mastery domains of the Chronic Respiratory Disease Questionnaire [38]. Measures of anxiety are strongly correlated with measures of social isolation, suggesting that COPD patients with anxiety withdraw from social interactions [39].

Psychological disturbances also contribute to the economic burden of the disease, since the proportion of patients relapsing within 1 month following presentation to an emergency department with an acute exacerbation is higher among COPD patients with anxiety and/or depression [40]. The presence of anxiety and/or depression remains an important risk factor for re-hospitalisation within a 12-month period in COPD patients with poor health-related quality of life [41].

The impact of anxiety on the physical disability and mortality of COPD patients is less clear. The magnitude of anxiety-related symptoms is associated with self-reported measures of disability [30, 42], but not with objective measures of functional exercise capacity [14, 26]. One prospective longitudinal study reported that, at the time of LTOT prescription, poor emotional function was a significant predictor of survival in female COPD patients [43]. However, this domain did not predict survival in male patients, with the reasons for this discrepancy between sexes remaining to be established [43].

Screening and diagnosis

Several questionnaires are available for the quantification of anxiety-related symptoms. Questionnaires such as the Hamilton Anxiety Rating Scale [44], Beck Anxiety Inventory [45] and State–Trait Anxiety Inventory [15] exclusively measure anxiety symptoms. Other questionnaires, such as the Hospital Anxiety and Depression Scale [46], Hopkins Symptom Check List [47] and Patient Health Questionnaire [48], quantify multiple dimensions of psychological function and provide a subscore for anxiety-related symptoms. Despite the important contribution that psychological manifestations such as anxiety make to the morbidity associated with COPD, the uptake of these instruments in clinical practice appears poor [49–51]. Specific threshold values have been established for some of these questionnaires, which permit those individuals at risk of exhibiting an anxiety-related disorder to be identified [45, 46, 48]. However, these are screening rather than diagnostic instruments. The diagnosis of a specific anxiety disorder (DSM-IV) should be made by a qualified mental health professional *via* a structured clinical interview following the DSM.

Treatment

With the increasing awareness of the high prevalence and impact of anxiety-related symptoms in patients with COPD, it is interesting to note that psychological manifestations of COPD are treated in only a minority of patients [52].

Pharmacological therapy

Few studies have investigated the effectiveness of specific medications for anxiety in patients with COPD (table 1) [53–56]. ARGYROPOULOU *et al.* [53] performed a double-blind randomised crossover study to investigate the effects of buspirone, a serotonin receptor agonist, in patients with COPD. At the completion of a 14-day administration period (20 mg daily), subjects demonstrated a significant reduction in anxiety and dyspnoea and an increase in exercise tolerance. This finding contrasts with that of SINGH *et al.* [54], who failed to demonstrate any effect of buspirone on anxiety, dyspnoea or exercise tolerance following a 6-week administration period of doses ranging 30–60 mg daily. Furthermore, at these higher doses, 20% of patients experienced side-effects of nausea, diarrhoea, dizziness, fatigue, weakness and increased dyspnoea, causing them to withdraw from the study. BORSON *et al.* [56] reported that, on completion of a 12-week administration period of nortriptyline, a tricyclic antidepressant, COPD patients demonstrated a reduction in anxiety, as well as depression. SILVERTOOTH *et al.* [55] noted that citalopram, a selective serotonin reuptake inhibitor, did not change symptoms of anxiety or depression or self-reported physical function in COPD.

TABLE 1 Anxiolytic drug therapy in chronic obstructive pulmonary disease: summary of the published randomised trials

First author [Ref.]	Study design	Intervention	Measurement instruments	Results
ARGYROPOULOU [53]	Randomised double-blind placebo-controlled crossover trial (n=16)	Buspirone (20 mg) *versus* placebo for 2 weeks	Anxiety: Symptom Check-List-90-R Exercise capacity: 6MWD and WR_{max} achieved during incremental cycle ergometer testing	Reduced anxiety and depression Increased 6MWD and WR_{max}
SINGH [54]	Randomised double-blind placebo-controlled crossover trial (n=11)	Buspirone (30–60 mg) *versus* placebo for 6 weeks	Anxiety: State–Trait Anxiety Inventory Exercise capacity: 12MWD and WR_{max} achieved during incremental cycle ergometer testing	No significant differences in either exercise capacity or anxiety scores
SILVERTOOTH [55]	Randomised double-blind placebo-controlled trial (n=19)	Citalopram (20–40 mg) *versus* placebo for 12 weeks	Anxiety: Hamilton Anxiety Rating Scale	No differences between groups; however, citalopram tended to be more effective than placebo in patients with mild-to-moderate psychological symptoms
BORSON [56]	Randomised double-blind placebo-controlled trial (n=30)	Nortriptyline (increased over first 4 weeks to target dose of 1 $mg \cdot kg^{-1}$) *versus* placebo for 12 weeks	Anxiety: Patient-Rated Anxiety Scale	Reduced anxiety

Numbers of patients shown are those completing the trial. 6MWD: 6-min walking distance; WR_{max}: maximum work-rate; 12MWD: 12-min walking distance.

Nonpharmacological therapy

Psychotherapy, which includes cognitive behavioural therapy, has been applied in COPD patients in an attempt to minimise catastrophic cognitive processes associated with dyspnoea. Such therapy aims to reduce anxiety by stopping the dyspnoea–anxiety–dyspnoea cycle [35]. The few randomised controlled trials that have investigated the effectiveness of psychotherapy in COPD have yielded mixed results. Compared with a control group receiving no specific therapy aimed at alleviating anxiety, psychotherapy has been demonstrated to reduce anxiety in one [57], but not another [39], study. In patients with COPD, the addition of specific psychotherapy to a comprehensive 12-week pulmonary rehabilitation programme has been demonstrated to reduce anxiety over and above any change seen following comprehensive pulmonary rehabilitation alone [58].

Two randomised controlled trials have investigated the effectiveness of progressive muscle relaxation, a technique that promotes a reduction in tension in specific muscle groups, for anxiety in COPD [59, 60]. The progressive muscle relaxation was delivered by an instructor in the earlier study [59] and by a pre-recorded tape in the latter study [60]. On completion of the treatment sessions, the group that had undergone progressive muscle relaxation demonstrated changes in respiratory frequency, cardiac frequency [59] and skin temperature that met an arbitrary set of criteria established for the definition of relaxation [60]. However, the effect of progressive muscle relaxation on anxiety remains uncertain, with one study reporting no significant change over four treatment sessions [59], and the other concluding that the decreased anxiety reported by the treatment group resulted, at least in part, from regression to the mean [59, 60]. Progressive muscle relaxation offered in conjunction with breathing exercises and comprehensive disease-specific education, including strategies for panic control and stress management, is not effective in reducing anxiety [61].

In COPD patients, several studies have shown that pulmonary rehabilitation reduces anxiety [37, 39, 62–65]. EMERY *et al.* [66] demonstrated that supervised exercise training performed over 10 weeks, combined with education sessions that included stress management techniques, yielded significant reductions in symptoms of anxiety. In contrast, attendance at the education and stress management sessions without supervised exercise training did not improve anxiety, indicating that exercise training, rather than education, is the component of a comprehensive pulmonary rehabilitation programme capable of improving such symptoms [66]. Nevertheless, without adherence to an effective exercise maintenance programme, the longevity of any reduction in anxiety demonstrated on completion of a comprehensive pulmonary rehabilitation programme was <12 months [63, 67]. The addition of target-flow inspiratory muscle training to pulmonary rehabilitation did not confer additional benefit [68]. The effects of chronic disease self-management on symptoms of anxiety have not been established [12, 22].

DEPRESSION

Classification and diagnostic criteria

Feelings of depression in COPD have been described as reactive to the condition [69], and symptoms may range from an ''adjustment disorder with depressed mood'' to ''major depression'' [18]. An adjustment disorder is a psychological response to an identifiable stressor, such as a chronic disabling general medical condition. It is characterised by distress in excess of what would be expected from exposure to the stressor, resulting in a significant impairment in social functioning. A major depressive disorder is characterised by one or more major depressive episodes without manic episodes (table 2). Diagnostic criteria for minor depression, also known as subclinical depression or subthreshold depression [70], are awaiting validation before being officially included in the DSM [18]. A major depressive disorder must be distinguished from depressive symptoms associated with chronic illness, as there is no proof of an aetiological relationship between a major depressive disorder and COPD [71]. This point is important as it may determine patient management.

Prevalence in COPD

Irritability and hopelessness are frequent complaints in patients with COPD [72, 73]. In a systematic review of the literature, the prevalence of depression in patients with moderate-to-severe COPD ranged 7–42% [74], prevalences

TABLE 2 *Diagnostic and Statistical Manual of Mental Disorders* diagnostic criteria for a major depressive episode

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning
Depressed mood for most of the day, nearly every day, as indicated by either subjective report (*e.g.* feels sad or empty) or observation made by others (*e.g.* appears tearful)[#]
Markedly diminished interest or pleasure in all, or almost all, activities for most of the day, nearly every day (as indicated by either subjective account or observation made by others)[#]
Significant weight loss when not dieting or weight gain (*e.g.* a change of >5% of body weight in 1 month), or decrease or increase in appetite nearly every day
Insomnia or hypersomnia nearly every day
Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
Fatigue or loss of energy nearly every day
Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observation by others)
Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

[#]: at least one of these symptoms should be present. Symptoms that are clearly due to a general medical condition should not be included. Reproduced from [18] with permission from the publisher.

supported by subsequent studies [52, 75, 76]. High rates of depression (25–30%) were noted after hospitalisation for COPD exacerbation [25]. As with symptoms of anxiety, the uncertainty regarding the prevalence of depression stems from the heterogeneity of the populations and the measurement properties of the questionnaires used [74, 77].

Screening questionnaires for depression in elderly people may be less precise since they include somatic items that may occur as part of the ageing process, with the consequence of overestimation of the prevalence of depression. The geriatric depression scale was specifically developed to overcome these limitations [78]. Using this questionnaire, it was found that, in a population of patients with severe oxygen-dependent COPD, 57% (95% confidence interval 47–66%) demonstrated significant depressive symptoms and 18% (95% confidence interval 12–27%) were severely depressed [79].

Risk factors

Although depression in COPD is more prevalent than in an age-matched general population, a number of confounders exist. These include the lack of social support that is found among elderly and chronically ill individuals and their past psychiatric and medical history, as well as their low socioeconomic status. Findings from community studies evaluating socioeconomic status as a risk factor for depression are mixed [80]. More severe COPD usually correlates with higher depression scores on screening instruments [29, 31, 81]. The long-term use of systemic corticosteroids has also been related to depression in COPD [82]. In primary care, depressive symptoms correlated with dyspnoea and female sex, and inversely with body mass index [83]. It is probable that continuing smokers with COPD are more at risk of depression than those who quit [84]. An increased risk of depression was found among patients with a higher educational level and among females with higher income [85].

Mechanisms

Although the primary impairment is pulmonary, the secondary emotional responses to chronic respiratory disease contribute greatly to the resulting morbidity. Dyspnoea, inactivity and the subsequent deconditioning result in further inactivity, social isolation, fear and depression [86]. In addition, patients with COPD experience losses in several areas of their lives. They may feel useless, experience reduced sexual activity, depend on others for their personal care and lose interest in future projects. In reaction, many regress to focusing their energy on their condition.

Although there is a relationship between smoking and depression, the underlying mechanisms remain unclear [87]. Tobacco may provide psychological relief for some individuals [88], and smoking cessation is associated with an increased rate of depression [89]. Little is known regarding the contribution of chronic hypoxaemia and LTOT to symptoms of depression.

Several authors have investigated the relationship between chronic hypoxia and neuropsychological function [90–92]. However, in these studies, neuropsychological function was defined by performances such as abstracting ability, perceptual–motor integration and coordination, and did not include depressive symptoms. LTOT may reduce mobility and social interactions. Unfortunately, both of the landmark multicentric studies of LTOT in the management of chronic resting hypoxaemia in COPD [6, 7] were conducted before the development of disease-specific health-related quality-of-life questionnaires that might have captured small but important changes in quality of life and emotional function. Given the increased survival effect of LTOT in hypoxaemic COPD patients, such trials cannot be repeated to more closely evaluate the possible improvement in quality of life.

Clinical features and impact

According to the DSM-IV, individuals with a depressive episode frequently present with irritability, tearfulness, brooding, obsessive ruminations, anxiety, phobia and excessive worry over their physical health [18]. Therefore, depressive disorders in COPD may be difficult to recognise if the symptoms and signs of depression are attributed to the underlying lung disease [93]. The patterns of depression in chronic illnesses may differ from one condition to another [94]. COVINO *et al.* [95] found that patients with chronic respiratory diseases were more likely to include low self-esteem, high apathy and high denial of impulse life in their depression. The predominant features of depression in COPD may also influence the selection of antidepressant drug therapy.

Depressive symptoms are associated with substantial impairments in the psychological, physical and social functioning that determine quality of life [38, 76, 81, 96]. In a study of depression in severe COPD, LACASSE *et al.* [79] noted marked impairments in all the domains of the 36-item Short-Form Health Survey (SF-36), a generic health-related quality-of-life measure. The scores were lowest in the domains related to physical function, but showed a moderate correlation in seven of the eight domains of the SF-36. Whether depressive symptoms are linked to hospital readmission following hospitalisation for an acute exacerbation is not clear. Although in two studies depression was not related to readmission during the year following an index hospitalisation [41, 97], in the study of NG *et al.* [97], depressed patients showed a greater length of stay during the index hospitalisation than nondepressed patients. The total number of days spent in the hospital over 1 yr was significantly greater in depressed than in nondepressed patients [97].

Screening and diagnosis

As there are no laboratory findings that are diagnostic of depression, increased awareness of healthcare providers is an important initial step in the diagnosis of this condition. In addition, screening questionnaires may identify high-risk patients [48–50]. MULROW *et al.* [98] systematically evaluated the usefulness of nine case-finding instruments in identifying patients with major depression. All are written at an easy or average reading level, and most can be self-administered within 5 min. The sensitivity of the questionnaires was 84% and the specificity 72% [98]. The authors could not identify any significant differences between the instruments. However, study subjects only comprised primary care patients attending a clinic and did not include those with specific psychiatric diagnoses.

Other instruments have been evaluated since the publication of the above review [48, 99], including one developed specifically

for use in COPD [100]. Unfortunately, there is very limited information regarding the use of routinely administered screening questionnaires for depression, or whether their use impacts on the detection, management or outcome of depressive symptoms [101]. If screening questionnaire results are positive, diagnostic confirmation by mental healthcare professionals or by primary care physicians trained in mental health can be made with high reliability [102]. The screening questionnaires should enable the clinician to identify those who need to undergo a more intensive diagnostic interview [98].

Treatment

Several studies have demonstrated that depression often remains untreated in patients with COPD [52, 79], in keeping with the observation that many elderly patients with comorbid conditions and chronic medical diseases are undertreated [103]. Time constraints, communication problems, patient preferences and the priorities of the healthcare professional contribute to the difficulties in effectively addressing more than one problem in any patient. Psychological distress may also be present in close family members, or other caregivers, who themselves may benefit from education and psychological support.

Pharmacological therapy

Pharmacological therapy must be considered when major depression is recognised. The ideal antidepressant for use in the typical elderly COPD patient should have a low side-effect profile, a short half-life and no active metabolites [93]. It would provoke few drug interactions and could be given once or twice a day [93, 104]. The choice of antidepressant also depends on the pattern of depression [95] and, especially in patients with chronic respiratory conditions, should not include sedation. Although respiratory depression is an important potential side-effect of psychotropic medications, the older antidepressants seem to have had little effect on ventilatory drive [105]. No report of such effect is available for the selective serotonin reuptake inhibitors and the newer antidepressants (venlafaxine, duloxetine or mirtazapine).

Previous small placebo-controlled trials of antidepressant drug therapy in patients with COPD did not demonstrate significant treatment effects on depression or quality of life (table 3) [56, 106–110]. This situation may be explained by several factors. In two studies [56, 111], depressive symptoms were not required for inclusion. The validity of most health status measurement instruments used in these trials has not been clearly established, and those that were used were generic or case-finding instruments unlikely to detect the small but clinically important changes over time [104]. Despite the small number of patients (underpowered), the finding of large significant differences in the emotional function and mastery domains of the Chronic Respiratory Disease Questionnaire indicated that paroxetine is highly active in COPD [109], even though the differences in the dyspnoea and fatigue domains were not significant. Evaluating the efficacy of antidepressant drug therapy in COPD-associated depression is clearly an important area for future research.

Nonpharmacological therapy

Pulmonary rehabilitation has gained wide acceptance in the management of COPD, since it improves health-related quality of life [111]. With few exceptions [66, 112], symptoms of depression were rarely addressed in the above randomised trials. When they were, significant improvements in the severity of depression scores were noted following 8–10 weeks of rehabilitation. The results of pulmonary rehabilitation are not affected by baseline psychosocial factors, and those with less favourable psychological or sociodemographic conditions also benefit from pulmonary rehabilitation [113]. It is unclear as to which components of pulmonary rehabilitation are most effective in alleviating depression. Psychotherapy added to physical therapy and educational sessions improved depression scores [58]. Compared with a 2-h education session, a 2-h session of group cognitive behavioural therapy also improved depression scores [57]. Further studies are clearly warranted.

Outcome

When depressive symptoms are identified in hospitalised patients, the prognosis is usually good and such symptoms usually remit within 12 weeks. However, only a quarter of those with major depression show remission by 12 weeks and only a half by 24 weeks [114]. In a cross-sectional study of 101 patients with severe COPD, depressed patients were twice as likely to refuse resuscitation as nondepressed patients [115]. Since depression may influence decisions related to end-of-life issues, issues of informed consent and capacity to understand the consequences of accepting or refusing a particular treatment must take into consideration the patient's mental state. If a patient is diagnosed with depression, then it should be treated before any potentially negative life-affecting decisions are made. Most evidence indicates a worse mortality among patients with COPD and depressive symptoms [87, 97, 116]. After controlling for the chronicity and severity of COPD, comorbid conditions and socioeconomic variables, NG *et al.* [97] reported that depressive symptoms were associated with a two-fold increase in mortality at 1 yr of follow-up. One small study reported a protective effect of depression on mortality [117].

WHEN TO REFER

Every clinician caring for patients with COPD should have a high level of suspicion regarding the presence of anxiety and depressive symptoms, as well as the possibility of a major anxiety or depressive disorder. Simple screening questionnaires, especially when self-administered, may therefore be of value in case finding and identifying patients requiring a more detailed evaluation. Many family physicians are comfortable in assessing these symptoms, prescribing psychotropic drugs and providing psychological support. Although respiratory specialists usually focus on the physiological aspects of the disease, they often have access to rehabilitation programmes within which a psychological assessment can be conducted. From a 1998 survey of pulmonary rehabilitation programmes in Canada, 43% of the outpatient programmes surveyed involved social workers in the interdisciplinary team, and 9% involved psychologists [118]. In an update of this survey, this proportion had increased to 61% for social workers but was not reported for psychologists [51]. Referral to a mental health professional is indicated when: 1) symptoms of anxiety or depression are highly positive on simple diagnostic screening; 2) anxiety or depression are refractory to pharmacological or nonpharmacological therapy; 3) the choice of anxiolytic or antidepressant drug is complicated by concurrent medications

TABLE 3 Antidepressant drug therapy in chronic obstructive pulmonary disease: summary of the published randomised controlled trials

First author [Ref.]	Study design	Intervention	Measurement instruments	Results
GORDON [106]	Randomised double-blind crossover trial (n=6)	Desipramine *versus* placebo for 8 weeks	Depression: Beck Depression Inventory; Zung Self-Rating Depression Scale	Both treatments (desipramine and placebo) led to a significant improvement in depression scores
LIGHT [107]	Randomised double-blind crossover trial (n=9)	Doxepin *versus* placebo for 6 weeks	Exercise capacity: 12MWD Depression: Beck Depression Inventory Anxiety: Spielberger's State–Trait Anxiety Inventory	No significant differences in either exercise capacity or psychological scores were observed
BORSON [56]	Randomised double-blind parallel groups trial (n=30)	Nortriptyline (n=13) *versus* placebo (n=17) for 12 weeks	Exercise capacity: 12MWD Dyspnoea: Pulmonary Functional Status & Dyspnoea Questionnaire Depression: Hamilton Depression Rating Scale Anxiety: Patient-Rated Anxiety Scale	Nortriptyline treatment was accompanied by improvements in anxiety, certain respiratory symptoms and day-to-day function; physiological measures remained unaffected. The clinical significance of these changes is unknown
STRÖM [108]	Randomised double-blind parallel groups trial (n=26)	Protriptyline (n=14) *versus* placebo (n=12) for 12 weeks	Dyspnoea: 6-point scale developed for the purpose of the study Quality of life: Sickness Impact Profile Anxiety and depression: Mood Adjective Check List; Hospital Anxiety and Depression Scale	No significant difference in quality-of-life questionnaire scores in either of the two treatment groups; neither proptriptyline nor placebo had any impact on the dyspnoea score
LACASSE [109]	Randomised double-blind parallel groups trial (n=15)	Paroxetine (n=8) *versus* placebo (n=7) for 12 weeks	Quality of life: Chronic Respiratory Disease Questionnaire	In the *per protocol* analysis, statistically and clinically significant improvement favouring the active treatment in the emotional function and mastery domains of the Chronic Respiratory Disease Questionnaire
			Depression: Geriatric Depression Scale	No significant difference in depression scores
EISER [110]	Randomised double-blind parallel groups trial (n=23)	Paroxetine (n=11) *versus* placebo (n=12) for 6 weeks	Quality of life: St George's Respiratory Questionnaire Exercise tolerance: 6MWD Depression: Hospital Anxiety and Depression Scale; Beck Depression Inventory; Montgomery–Asberg Depression Scale	No significant difference in either exercise capacity or psychological scores was observed

Numbers of patients shown are those completing the trial. 12MWD: 12-min walking distance; 6MWD: 6-min walking distance.

or comorbid conditions; and 4) the patient presents with suicidal ideation. Given that most medical illnesses are influenced by the psychological responses and coping mechanisms that patients use, a healthcare professional with mental health training may be invaluable in establishing those in whom the response is disproportionate to their underlying COPD. Whether patients with a history or family history of psychiatric disorders might be predisposed to developing anxious or depressed responses, and whether these responses are especially difficult to treat among those with pre-morbid conditions, remains to be evaluated. However, it is likely that an improved understanding of the psychiatric history in patients and their families, as well as the role of anxiety or depressive reactions to illness, will influence the management of psychological impairments and ultimately improve health-related quality of life.

CONCLUSION

Anxiety and depressive symptoms are common in patients with chronic obstructive pulmonary disease. Regardless of whether they are considered separately or as a combined construct, these symptoms adversely affect health-related quality of life and are likely to contribute to the physical disability and economic burden resulting from the disease. Factors such as cigarette smoke exposure, heightened experiences of dyspnoea, physical inactivity and social isolation, chronic hypoxia and long-term oxygen therapy may contribute to these psychological disorders in chronic obstructive pulmonary disease. Despite the increasing awareness of the prevalence and importance of anxiety and depressive symptoms in chronic obstructive pulmonary disease patients, the use of instruments specifically designed to screen for these features is not widespread. Although the optimal regimen for treating these disorders has not been established, supervised exercise training and appropriate pharmacological therapy are effective options.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge S. Martin for expert assistance in preparing this manuscript.

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