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Depression and anxiety in patients with COPD

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In the past two decades, there has been increasing recognition that patients with chronic obstructive pulmonary disease (COPD) with three or more comorbidities are more likely to be frequently hospitalized and may die prematurely compared to COPD patients without comorbidities [1]. Of such comorbidities, anxiety and depression contribute to a substantial burden of COPD-related morbidity, notably by impairing quality of life and reducing adherence to treatment [2]. Untreated and under-recognized depression and anxiety symptoms in patients with COPD have deleterious effects on physical functioning and on social interaction, increases fatigue and healthcare utilization [3,4]. Depression and anxiety are challenging to identify and treat because their symptoms often overlap with those of COPD [5]. Identifying depression, anxiety, and developing appropriate treatment strategies are critical to improve COPD patients' quality of life and reducing healthcare utilization. This editorial synthesizes the current understanding of the prevalence and potential mechanism of association, and discusses implications for treatment in patients with COPD with comorbid depression and anxiety symptoms.

What do we know about depression and anxiety?

Mental health related disorders are the leading causes of increased disability and impaired quality of life in older people worldwide. Specifically, mood disorders [major depression, dysthymias (chronic depressive symptoms of mild severity), minor depression, and anxiety disorders (generalized anxiety disorder, phobias and panic disorders) are common in patients with COPD [6,7]. The incidence of depression, in a recent longitudinal study by Schneider *et al.* (n = 35,000, COPD) with a follow-up of 10 years [7] was 16.2 cases per 1000 person-years in the COPD group compared to 9.4 cases per 1000 person-years in the non-COPD control group. In addition, those with severe COPD were twice as likely to develop depression [7, 8] compared to patients with mild COPD. To date there are no studies that have examined the incidence of anxiety disorders in patients with COPD in a longitudinal study. However, a recent cross-sectional study by Einser and colleagues [9] reported that COPD patients are 85% more likely to develop anxiety disorders compared to healthy, matched controls (controlling for confounding variables such as demographic characteristics and disease severity). In addition, the prevalence of clinical anxiety in COPD outpatients ranges between 13% and 46% [5]. Furthermore, COPD patients with comorbid anxiety

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disorders are twice as likely to exhibit self-reported functional limitations, poorer exercise tolerance and higher frequency of acute exacerbations compared to those without anxiety symptoms. Indeed, anxiety disorders are disabling and, unless adequately treated, they can become chronic, lower self-esteem, predispose to suicidal ideation, and increase the risk of hospitalization [5,6,8].

Mechanism of potential association with COPD

A recent systematic review and meta-analysis of 25 studies with long-term follow-up [8] revealed that the relationship between COPD and depression is likely bi-directional, as depression may be both a cause and a consequence of COPD. However, the exact mechanisms linking COPD with depression and anxiety have not been identified. The inter-relationship between smoking, depression and/or anxiety and COPD is unclear. Smoking increases the risk and severity of COPD, makes daily activities effortful and stressful, and increases the risk of depression or anxiety in patients with COPD. Associations between anxiety disorders and COPD appear to be largely explained by confounding factors such as previous history of cigarette smoking and nicotine dependence [10]. However, the relationship of mood disorders to COPD appears to be largely accounted for by nicotine dependence. Thus, these cross-sectional associations do not allow inference about causality but point out to the need for specifically designed studies. Depression and anxiety may lead to fear, panic, and hopelessness, low self- esteem, social isolation, and dependency on caregivers initiating a vicious circle that perpetuates anxiety and depression.

There is emerging evidence to suggest that low-grade chronic inflammation, mediates in part the association of depressive symptoms and pulmonary function. Increased inflammatory markers have been documented in both late-life depression [11] and COPD [12]. In a recent study of a population sample of older adults, elevated levels of the inflammatory biomarkers interleukin-6 and C-reactive protein accounted in part for the association of depressive symptoms with pulmonary obstruction [13]. In addition, there are biological, behavioral and social factors that may contribute to an increase in physical disability and social isolation in patients with COPD as illustrated Table.

A large study examined the prevalence of depression in COPD patients (n= 2118); (n= 335 smokers) without COPD; and (n = 243 nonsmokers) without COPD [14]. The prevalence of depression was 26%, 12%, and 7% of COPD, smokers, and nonsmokers, respectively. Its findings indicate that clinical and biologic markers were less important determinants of depression in COPD than disease symptoms and quality of life.

What are treatment options?

To date, the available evidence suggests that the effectiveness of treatment of depression or anxiety using the Selective Serotonin Reuptake Inhibitors (SSRIs) in patients with COPD is questionable. This is partly due to e.g. lack of adequate support by healthcare professionals, to explain to patients the reasons for and the efficacy of treatment; and/or to patients' fear that antidepressant drugs are addictive and have potential side effects. The collaborative care model (case management), with partnership with patients and family has been shown beneficial in the treatment of depression in patients with chronic diseases [15]. However, its

efficacy in COPD patients with comorbid anxiety or depression is unknown. A recent Cochrane [16] review highlighted pharmacological interventions for treatment of anxiety in COPD were inconclusive, because of the sub-optimal quality of trials and the non-significant results. Recently, a personalized, 9-session intervention (PID-C) was developed for patients with major depression and severe COPD [17]. PID-C is offered by care managers, who through support and targeted interventions help patients to work on their exercise regimens and take antidepressants. The care managers also collaborate with the patients' physicians in monitoring the patients' treatment and progress. A randomized controlled trial showed that PID-C led to higher remission rate of depression and greater reduction in depressive symptoms, and in dyspnea-related disability than usual care over 28 weeks and 6 months after the last session [18]. Low severity of dyspnea-related disability and adherence to antidepressants predicted subsequent improvement of depression. Exercise and low depression severity predicted improvement of dyspnea-related disability.

A recent systematic review [19] investigated the efficacy of comprehensive pulmonary rehabilitation (PR, exercise plus education) in patients with COPD patients and showed that reduction in level of depressive and anxiety symptoms in the short-term compared with usual care. In addition, a recent uncontrolled [20] intensive 3-week outpatient PR programme (6 hours per day for 5 days per week) showed significant improvement in depression and anxiety in patients with COPD. Again, the long-term benefits and their clinical significance require further investigation. Acute inpatient rehabilitation was followed by improvement of depressive symptoms and disability even in older patients with severe COPD and major depression. Improvement of depression was unrelated to the use of antidepressant drugs and was attributed to the behavioral interventions of pulmonary rehabilitation [21]. However, the long-term benefit of PR in reducing anxiety and depression is unknown. In addition, further work is required on the efficacy of maintenance therapy to alleviate these symptoms and achieve full remission.

There is some evidence to suggest that psychological therapy including cognitive behavioral therapy and counselling may improve depressive and anxiety symptoms in patients with COPD [5,6,]. However, currently there is uncertainty over the 'dosage' and the duration of therapy, even for the mild cases of anxiety and depression. In addition, there is limited availability of psychological therapy in primary care settings for this patient group. It is worth considering making the resources of psychological therapy available using web-technology as a supplement therapy.

Walters et al [22] examined the efficacy of telephone health mentoring using cognitive behavioral therapy [n = 80] versus usual care [n=74] in a 12-month treatment programme. The experimental group received 16 × 30 minutes over 12 months, with increasing time between calls. The control group received usual care provided by their general practitioners and a monthly phone call by a research nurse. Anxiety decreased in both groups at 12 months. Health mentoring improved the capacity for self-management but the two groups had similar scores of quality of life at the end of the treatment phase. Moreover, there was no difference in depression scores between the two groups. Bucknall and colleagues [23] reported that a minority of COPD patients who could learn to implement self-management

effectively were younger, and were more likely to be living with others. These patients had a significantly reduced risk of COPD readmission.

Barriers to treatment of interventions

The available evidence suggests that less than one third of COPD patients with comorbid depression or anxiety are receiving appropriate treatment for this. Factors that contribute to the lack of provision of treatment are multi-factorial. Maurer and co-workers [6] in their elegant review have reported the multistage barriers for detection and treatment of anxiety and depression in patients with COPD. These include i) patient perceived barriers (e.g. lack of knowledge, reluctance to disclose symptoms of anxiety or depression) ii) physician perceived barriers (e.g. lack of standardized diagnostic approach for anxiety and depression, short-consultation time and lack of confidence to pursue in-depth psychological assessment and iii) system-level barriers (e.g. poor communication between primary care and mental health systems, and lack of adequate resources for mental health treatment). In order to address these barriers an integrated treatment approach is required from the healthcare professionals, patients and caregivers. In addition, the healthcare providers should be ready to provide appropriate resources to improve the quality of service provision and clinical practice.

Current screening tools for anxiety and depression in patients with COPD were primarily validated for patients with other chronic diseases. The Hospital Anxiety Depression and the Beck Depression and Anxiety Inventory scales have been recommended as the preferable choice of screening tools for anxiety and depression in patients with COPD [6]. However, some of the items in these scales contain somatic symptoms, which make it difficult to decipher because of the overlap symptoms of COPD and depression or anxiety. Thus, designing disease-specific anxiety and depression scales for patients with COPD is a worthy future endeavor.

Challenges for research and clinical practice

There is little evidence to suggest whether routine screening (which is resource intensive) may improve treatment for anxiety and depression in patients with COPD. Therefore, healthcare professionals should play an active role, at least for those identified with clinical depression and anxiety, to ensure appropriate treatment, and to monitor its efficacy.

However the lack of strong evidence for the efficacy of antidepressant drug therapy in patients with COPD with comorbid depression and anxiety, necessities well-controlled clinical trials to explore efficacy of antidepressant drug therapy in inducing sustained remission. In addition, there is very little evidence to show to the healthcare providers (payers) that treatment is cost effective and/or reduces healthcare utilization.

At the moment, PR programmes do not provide special provision for COPD patients with clinically significant anxiety and depression and whether interventions that are specifically targeted (designed) by the severity of respiratory impairment, gender, culture and duration of illness may have impact in terms of prognosis is worthy of investigation.

Conclusion

Untreated comorbid anxiety and depression in patients with COPD have devastating consequences, overwhelm the coping strategies of COPD patients and their caregivers and may increase healthcare utilization. There are some promising findings regarding pulmonary rehabilitation, smoking cessation, psychological and antidepressants drug therapy in reducing anxiety and depressive symptoms in patients with COPD. However, these findings require further testing to examine their efficacy in well-controlled, randomized controlled trials, with larger samples and long-term follow-up.

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Table

Association, symptoms, impact and treatment options for depression and anxiety in COPD

Association and clinical implications

- Elevated systemic inflammation e.g. Interleukin 6, C-Reactive Protein
- Use of long-term oxygen therapy
- Increase in the number of comorbidities
- Increase consultations with general practitioners
- Morbidity and mortality
- Female gender
- Severe respiratory impairment
- Cachexia

Symptoms

- Health endangering behavior (smoking)
- Increased fatigue
- Panic
- Social withdrawal
- Lack of interest in pleasurable activities
- Fear
- Dyspnoea on exertion
- Insomnia
- Somonolence

Impact on physical and social functioning

- Reduced exercise capacity
- Increased physical disability
- Reduced social interaction
- Dependency on caregivers
- Emotional liability
- Loss of social role
- Loss of libido
- Decrease in cognitive functioning
- Early retirement from work
- Loss of self-esteem

Treatment options

- Support and adherence enhancement to exercise and antidepressant treatment
- Pulmonary rehabilitation
- Personalized intervention
- Counseling
- Exercise
- Relaxation therapy
- Antidepressant drug therapy
- Psychotherapy (Cognitive behavioral, supportive)

- Yoga
- Social support and respite care for caregivers
- Telephone health mentoring using cognitive behavioral therapy