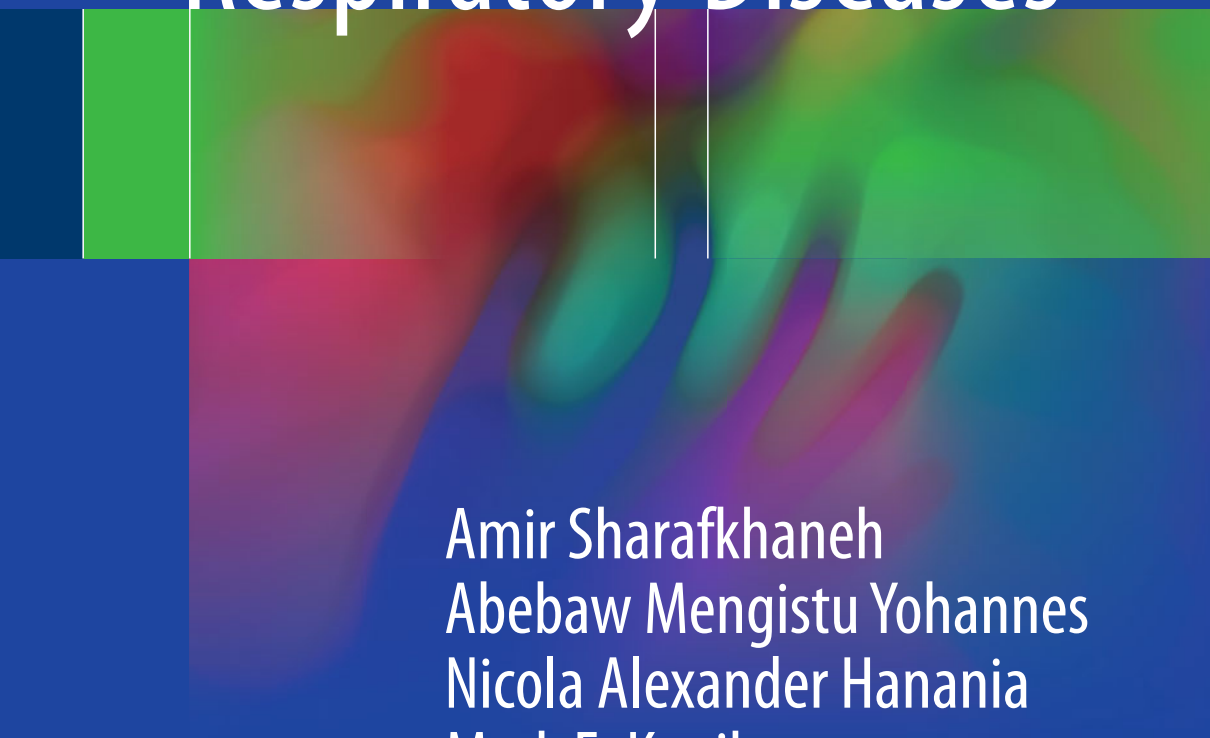
Depression and Anxiety in Patients with Chronic Respiratory Diseases



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Preface

As populations age, the prevalence of chronic respiratory conditions increases steadily. Further, recent advances in various health-related fields have been extending human longevity. Undoubtedly, chronic medical conditions, with no exception for chronic respiratory conditions, affect quality of life negatively and result in various psychiatric conditions including depression and anxiety. Thus, as the prevalence of chronic medical conditions increases, the prevalence of associated psychiatric conditions increases too. In this book, we aim at evaluating various chronic respiratory conditions associated with psychiatric comorbidities and explore the management options available. Chapters 1–8 are dedicated to psychiatric conditions in various respiratory problems. In Chap. 1, Drs. Rose and Sharafkhaneh provide a general overview of respiratory conditions and how they promote depression and other psychiatric comorbidities. In Chap. 2, Drs. Dooley and Kunik review depression and anxiety across various age groups. In Chap. 3, Drs. Yohannes and Willgross discuss various tools that are used to assess depression and anxiety. Drs. Majid and Nadim, in Chap. 4, focus on chronic obstructive pulmonary disease (COPD) and depression. In Chap. 6, Drs. Malatack and Barto explore depression and anxiety in patients with cystic fibrosis. Dr. Sista and colleagues, in Chap. 7, focus on psychiatric conditions in end-stage lung disease and lung transplantation. Finally, Drs. Hasmi and Khawaja explore psychiatric conditions in sleep disorders. The second part of this book focuses on management strategies including pharmacological and non-pharmacological interventions to treat depression and anxiety in patients with chronic respiratory conditions. Chapter 10, by Drs. Hynninen and Nordus, brings our attention to non-pharmacological intervention while Chap. 11, by Drs. Yohannes and Leroi, focuses on medication for depression and anxiety. At last, Drs. Ponti and Braun explore end-of-life issues in patients with advanced respiratory conditions. We hope that this collection of chapters from practitioners and researchers with different medical backgrounds can

provide a solid basis for clinicians who take care of patients with chronic and advanced lung diseases. We would like to thank the staff at Springer for their tremendous help to make this project successful.

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Chapter 1
Overview of Psychological Considerations in the Management of Patients with Chronic Respiratory Conditions

Mary Rose, PsyD and Amir Sharafkhaneh, MD, PhD

Introduction

Mood disorders are often eclipsed by the primary task of respiratory management in those with chronic respiratory diseases. This is likely for a variety of reasons, including that it is not the forte of the primary respiratory provider to identify and/or manage these symptoms, that the presenting problem *is* the respiratory illness itself and that resources to identify and manage quality of life issues and mood disorders are often lacking. Though pharmacological options are generally readily available, identification of the mood disturbance is, in itself, time-consuming and requires some expertise to properly identify. Additionally, resources of psychotherapists with expertise in behavioral medicine are lacking.

The largest of psychosocial problems faced by those with respiratory illnesses might be the same issues as those faced by any patient facing significant medical challenges. Though there may be some common psychosocial difficulties between the patients who share specific medical disorders, to some degree, individual differences with regard to resilience, coping strategies, comorbid complications, disease manifestation, hardiness, meaning attributed to the disease, and psychosocial supports all influence the direction and toll the disease itself may take on the individual. Lazarus describes a pattern of appraisal which is critical to any stressors; this involves the person evaluating the threat of the stress as well as the resources they need to minimize, tolerate, or eradicate the stressor. This appraisal process is critical to the patient's future steps of how to rally resources to address the needs for

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managing the illness. It is at this stage that the patient is in vital need of resources to facilitate decision making and that they are vulnerable to decompensation in decision processing if they cannot rally these resources.

In order to create a sensitive picture of how medical disorders affect psychological status as well as how psychological functioning can drive the course and progression of medical conditions, we need to consider several factors. This include not only how the social circumstances of the disease and fears related to prognosis and disability affect one, but how the disease process itself can affect mood and coping resources, and how the disease modifying treatments themselves may also drive psychosocial factors. This is particularly important in diseases such as asthma which are known to have a direct physiological effect on the generation of anxiety. Recognition of mood disorders with chronic illness is further critical as depression and/or anxiety may interfere with adherence to treatments, though this relationship has interestingly not been clearly shown [1]. Overall, those with respiratory disease have higher prevalence of concurrent depression or anxiety disorders compared with those without respiratory disease. However, a history of respiratory disease does not appear to be associated with increased risk of new onset of depression or anxiety disorders [2]. This would suggest that the disease process itself does not significantly drive the development of mood disorders.

One factor, becoming more difficult to control in research, is that newer disease-modifying drugs as well as CAM are more accessible, and are being more rapidly developed. This makes progression and direction of disease in some patients dramatically different than those of others, who may have either been sick longer, had less access to care at critical times of their treatment, or accessed additional therapeutics into their care. Thus, generalization about how specific medical conditions affect mood and psychosocial status is far more complex.

Psychological Basis for Depression and Anxiety in Chronic Medical Condition

Mood disorders can be broadly examined as those features which are depressive and those which are more anxiety-focused experiences. Unipolar depression is most likely to take the form of unhappiness and lethargy of thought and action, loss of interest or pleasure, decreased energy, disturbance of sleep and/or appetite, and concentration difficulty. More serious symptoms include the following: feelings of guilt or low self-worth, helplessness, and hopelessness. Depression is often associated with anxiety as well, particularly in the active stages of treatment, when patients are more vulnerable to acting upon suicidal impulses. Anxiety disorder symptoms are most often exhibited as overly activated feelings or unease, and sensations of being unable to wind down and/or hyperarousal emotionally, cognitively, and/or physiologically. Overall, anxiety is represented by a feeling of diminished control over one's self or surroundings.

The 12-month prevalence of a depressive episode in the USA in 2010 was 6.9% [3]. Causes for depression, however, are multifactorial, and there are very few population-based studies examining how these factors predispose one to depression or how they influence the course of the disease.

Depression and medical disorders are increasingly recognized as being bidirectional. Patients with unipolar depression have been found to die 5–10 years earlier than patients without depression [4]. Patients with depression and other psychiatric illnesses often develop illnesses such as vascular disease, diabetes, chronic obstructive pulmonary disease (COPD)/asthma, and cancer at an earlier age than others. Across the board, those with bipolar illness have been found to have a greater number of medical complications as well as increased mortality [5, 6]. One study showed a dose–response-type relationship between panic and asthma, and bidirectional longitudinal associations between the two conditions [7]. These associations have been attributed not only to maladaptive health behaviors which are more common in those with psychiatric illnesses, but also to the physiologic effects of psychiatric illness.

The role of depression as an overall health risk is becoming more widely accepted. The American Heart Association (AHA) has released a statement elevating depression to the status of a risk factor for those with acute coronary syndromes "the preponderance of evidence supports the conclusion that depression after acute coronary syndrome is a risk factor for all-cause and cardiac mortality, as well as for composite outcomes including mortality or nonfatal cardiac events. As such, depression should be elevated to the level of a risk factor for poor prognosis after acute coronary syndrome by the American Heart Association and other health organizations" [8].

One study reviewed 16 studies on depression or anxiety as predictors of COPD outcomes. These studies suggested that the presence of depression or anxiety consistently increased the risk of having poor COPD outcomes [9]; comorbid depression increased the risk of mortality [9]. The authors noted that psychologic distress increased the risk of COPD outcomes/mortality in most of the studies they reviewed. With regard to causation, COPD consistently increased the risk of depression [9], indicating a directional factor to the psychological status and health condition.

Dysphoria Associated with Diagnosis

Perhaps the most salient response to diagnoses with a distressing illness is often not the specific illness but individual differences with regard to resilience and how one perceives the meaning and challenges of the illness. In some ways, the most important aspect of how one experiences illness may be whether the existential question is framed as *why me* versus *why not me*. Both issues may be expressions of adaptive or maladaptive coping depending upon how the individual answers this question for themselves.

Why me is a common question from those facing a newly diagnosed medical illness. The question is often associated with disbelief and sadness that there may be spiritual reason that illness develops. However, such a question may also be protective in that it could suggest that the person recognizes that the health condition may in part be bad luck and/or unfair. Thus, as a diminishing component to one's identity, it is not readily accepted. Rather, the illness is given a controlled space in the individual's life where it can be monitored and kept at bay. Dangers of grappling with this question are that the individual may become stuck in a search for meaning where there is none to be found. There is also a risk that he/she may fail to integrate the necessary steps to manage the illness.

Why not me often arises less acutely, and sometimes not at all rather than a question the fairness of a medical diagnosis, asking this question could be seen as a diminutive acceptance that the illness is just. However, it more likely arises as a way of accepting the challenge as reasonable, given one's risk factors or lifestyle. This question may also serve to reinforce that the illness may be random or unfair, and thus equally distributed. On a more sophisticated level, it may also be a way through which the patient reinforces to him/herself their ability to take on, manage, overcome, and/or integrate the disease into his/her life.

The biobehavioral and social factors which affect the course of a serious health condition and the ways in which lifestyle, coping, and longevity are likely to be impacted are likely modified by numerous factors.

Individual-specific factors include the following: resilience, presence or absence of psychopathology, medically comorbid conditions, general health behavior, optimism level, comprehension of the disease, previous exposure to the illness (familiarity), substance reliance (alcohol, tobacco, and illicit substances), stage of life when the illness develops or is diagnosed, locus of control, pain tolerance, self-efficacy, ability to utilize care (adherence), career, faith (religion, in others, etc.), frustration tolerance, and the burden of specific symptoms such as fatigue, degree to which the illness physically or mentally impacts the patient or threats identity or is associated with pain (e.g., change in strength, physical appearance, and vision). We conceptualize these factors visually as a funnel through which the individual characteristics are squeezed to determine perceived health quality and quality of life, and ultimately the disease course (see Fig. 1.1).

The presence of more serious symptoms of depression such as feelings of helplessness and hopelessness is also likely to negatively impact coping and outcomes.

External or social factors would include the following: access to care, social supports, *social status* of the disease being faced, understanding by care providers of the etiology of the disease, how the family reacts to the disease, limitations on the disease, how its treatments or the diagnosis itself impinges on career/job performance, and ability/resources to follow through with care (insurance benefits and transportation).

The above may dramatically drive the course of a disease in the individual. For example, a patient diagnosed with multiple sclerosis with significant Uhthoff-related disability (heat intolerance) would be expected to face the

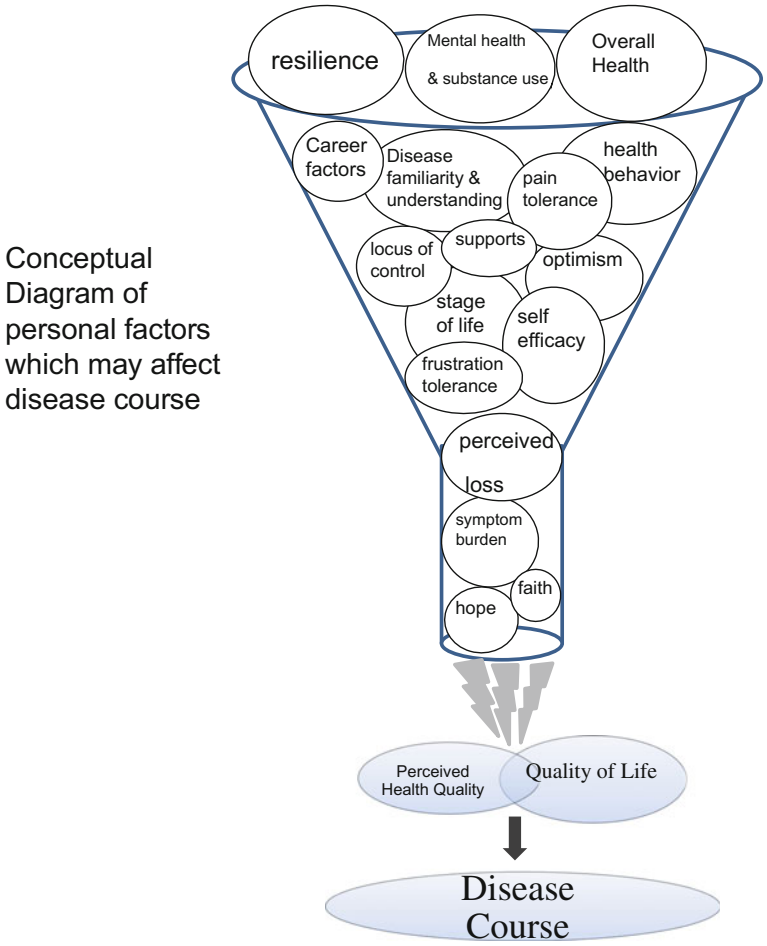

Fig. 1.1 Conceptual diagram of personal factors which may affect disease course

anticipation of disease management better if she lived in a cool climate, worked in an air-conditioned building, with low perceived psychosocial stress, resources to work part-time and access to physical exercise options, than would a steel worker who is the sole income earner for her family and with minimal resources. However, it is critical to remember that the weight of each of these factors will differ and despite all risk factors pointing to a patient being high or low risk, any single factor may tip one to an adaptive or maladaptive coping response, disease course and outcome.

Older people are often less dramatically impacted by new medical diagnosis, apparently because they have had more extensive history with health-related problems than the young, and because new health problems are less likely to be perceived as dramatically altering activities of daily living than for the young.

Some research suggests that the concept of unmet needs may affect this, as older cancer patients appear to cite unmet needs as less impactful to them than do younger patients [10].

There are several sources of mood disturbance in those struggling with chronic respiratory illnesses. Patients may have preexisting mood disorders, but they may also develop a reactive mood disorder consequent to the limitations caused by their respiratory illness.

In patients hospitalized for COPD, 30-day mortality rates were significantly higher in those with depression and anxiety diagnosis [11]. Willgoss et al. reviewed 10 studies (out of 410 examined) which met criteria for review if prospective, included diagnosed anxiety disorders from a clinical interview using an established psychiatric format, and published in English. Their review suggested that the presence of clinical anxiety was quite high in those with COPD ranging from 10 to 55% (median 17%) in all subject samples [12]. They note that social phobia and specific phobia were particularly prevalent.

Neither the presence of a significant medical condition nor its severity is necessarily associated with the experience of grief, anxiety, or dysphoria. Numerous studies have examined the presence of mood disorders in medically compromised populations but getting to the answer of why some patients are more vulnerable and a reliable model for identifying at-risk patients has been notoriously elusive. It appears that no single factor consistently dictates the course of medical illness. This suggests that it is imperative to carefully evaluate patient risk and protective factors and to tailor treatment to the individual.

Physiological Basis for Depression and Anxiety in Chronic Medical Condition

A properly functioning respiratory system maintains a constant supply of O_2 in the cells and removes CO_2 to assist in the regulation of blood acidity. Chronic medical conditions not only affect these functions but also negatively affect other body systems that work in coordination with the respiratory system. Disruption of proper respiratory function may negatively impact central nervous system (CNS) function and promote depression and anxiety beyond the effect that any chronic condition has on mood due to impaired quality of life.

Chronic respiratory conditions specifically predispose one to low levels of blood oxygen. Delivery of O_2 to cells, including brain cells, is compromised when arterial partial pressure of oxygen declines below 58 mmHg. With the progression of chronic respiratory conditions, oxygenation declines initially during exertion and sleep. However, with progression of the disease, patients remain hypoxic constantly with worsening hypoxia during sleep and exertion. Further, with worsening respiratory disease, gradual chronic retention of CO_2 occurs.

In addition to several functional and psychological reactionary bases for depression in patient with chronic respiratory condition (see prior section), physiological derangements resulting from chronic respiratory conditions may cause structural changes in CNS and promote depression due to organic causes. Giltay and colleagues in a longitudinal follow-up of a large cohort showed that low lung volume was associated with increased risk of depressive symptoms in future [13]. Similarly, the prevalence of depressive symptoms was higher in COPD patients with severe lung function impairment [14].

The main question that is not answered is to what degree organic issues related to chronic respiratory conditions promote depression versus the quality of life and nonorganic issues resulting from chronic respiratory conditions.

Hypoxia (both chronic and intermittent) affects the production of various neurotransmitters at the level of central and peripheral nervous systems [15]. Among respiratory conditions associated with hypoxia including sleep-disordered breathing, lower airway diseases, and lung parenchymal diseases, hypoxia is a unifying phenomenon. One of the phenomena examined in the depression literature is "vascular depression." As an individual ages, the prevalence of MRI-defined subcortical hyperintensities rise as the prevalence of depression rises. Considering that patients with chronic respiratory conditions usually are older and have higher prevalence of cardiovascular and metabolic conditions (diabetes and obesity), it is likely that hypoxia (continuous or intermittent) on the background of cerebrovascular diseases will intensify the local hypoxic conditions and produce more structural changes (MRI-defined subcortical hyperintensities), and thus more predisposition to vascular depression. Interestingly, Van Dijk and colleagues, after adjustment for common risk factors of cerebrovascular disease, identified low O_2 and COPD as major risk factors for the presence of periventricular white matter change in a large sample of patients [16]. Role of hypoxia in causing depression is also shown in patients with sleep-disordered breathing [17]. In contrast to hypoxia, it is not clear whether hypercapnia exerts additional detrimental effect on cognition and mood despite higher prevalence of depressive symptoms in severe COPD.

Other potential organic mechanisms linking chronic respiratory conditions to depression are oxidative stress at the level of microvasculature. Forlenza and colleagues showed increased oxidative damage correlating with the severity of depression [18]. Similarly, oxidative stress was higher in patient with COPD [19]. Thus, it is likely that the exposure to a milieu with higher oxidative stress will promote depression in patients with COPD. However, effects of anti-oxidants on depression in patients with COPD are not known.

With advancement of pharmacotherapy, chronic medical conditions are managed with various combinations of medications. The medications improve symptoms and functionality. In many situations, they may also improve sleep quality and reduce hypoxia. Thus, lack of proper pharmacotherapy can contribute to depression in chronic respiratory conditions. In contrast, some of the therapies for respiratory conditions may result in jitteriness and disturb sleep, and thus may indirectly contribute to mood problems. However, optimization of medical therapy improves patient's quality of life and reduces symptoms, thus improving overall quality of life and mood.

Summary

Chronic medical conditions, through various mechanisms, may result in mood disorders. The higher prevalence of the mood disorders in these patients is multifactorial and includes the effects of chronic illnesses on quality of life and on ability of the affected individuals to function. In addition, severity of hypoxia plays a crucial role in promoting mood disorders. Some major questions which remain to be explored on the relationship between medical illness and psychological functioning include the following: what if any physiological component to the disease process itself increases risk for mood disorder, is there a kindling effect from dyspnea or air hunger, what are the protective or resilience factors against development of anxiety or depression with comorbid respiratory disease, and how can we provide intervention early on to prevent the development of mood disorders in patients who are vulnerable. An additional question is if we treat mood disorder symptoms more proactively and routinely, is the course of the disease itself altered. We believe that the likely answer to this will be yes.

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Chapter 2
Depression and Anxiety Across the Age Spectrum

Erin Dooley, MD and Mark E. Kunik, MD, MPH

Introduction to Anxiety and Mood Disorders and Their Symptoms

Careful consideration of mental illness in differential diagnoses and its inclusion in problem lists and treatment plans improve the effectiveness of care and patient outcomes, especially in the geriatric population. Mental health issues are frequently overlooked in this group because of the overlap of medical symptoms. The unfortunate result is a failure to optimize the treatment of both medical disease and mental illness. The persistent cultural and social belief that mood and anxiety symptoms are part of the normal aging process impedes diagnosis and management of these important and treatable problems. This chapter provides an overview of anxiety and mood disorders and symptoms, with particular attention to changes with aging. The discussion concludes with a review of treatment options and issues related to mental health care in the elderly population.

Symptomatology and Key Disorders

Anxiety and mood disorders are both associated with a wide range of symptoms, some of which may present differently in older as opposed to younger adults.

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Medical professionals in all fields should be familiar with these symptoms and their variable presentations according to age to detect mental health problems early and begin appropriate intervention or treatment.

Anxiety

Anxiety is a psychological and physiologic response to stress manifested in a feeling of dread or worry and associated with increased arousal. It is a biologically adaptive symptom but can graduate to a pathologic disorder if it becomes overwhelming or limits a person's functioning. Anxiety is distinct from fear in that it is a general feeling of ongoing distress as opposed to an acute emotional response to a perceived threat; but both anxiety and fear can manifest in physiologic symptoms, such as increased heart rate, palpitations, sweating, and other symptoms of autonomic arousal. Many medical conditions can cause symptoms of anxiety, and thus, it is necessary to rule them out prior to treatment of any anxiety disorder. Possibly because the typical age of onset of anxiety disorders is quite early (11 years) [1], these disorders in the aging population tend not to be readily recognized and treated. Additionally, anxiety is commonly comorbid with depressive symptoms, with attention predominantly focused on depression, compounding the issue. It is very important for symptoms to be detected and treated as anxiety, as it was recently suggested that even mildly elevated symptoms of worry are associated with future cognitive impairment [2]. However, considerable variation exists in prevalence estimates of most anxiety disorders. More research is needed to further investigate anxiety disorders in the aging population [3].

Key anxiety disorders in older adults include the following:

- Generalized anxiety disorder (GAD) is characterized by chronic excessive worry or anxiety. These feelings must occur most days for six months or more and cause significant impairment. GAD is frequently associated with comorbid psychiatric illness and in the elderly often progresses to depression or to a mixed disorder of both anxiety and depression [4]. Anxiety in older patients tends to follow traumatic events or threats, whereas depression more often follows loss events [5].
- Specific phobias feature an irrational, overwhelming fear of a certain object or situation and cause marked impairment. The patient recognizes that the fear is irrational and commonly avoids phobic stimuli. Exposure to the phobic stimulus can trigger panic attacks. Social phobia is another common phobia, also known as social anxiety disorder, which is specifically associated with an intense fear of social situations.
- Posttraumatic stress disorder (PTSD) is characterized by intense fear, helplessness, and horror after a traumatic event. The patient must have directly experienced or witnessed an event that involved threatened or actual death, injury, or threat to physical integrity. Patients have a persistent avoidance of stimuli associated with the traumatic event, as well as a re-experiencing of the

event that is associated with psychological distress; physiological reactivity to stimulus cues to the event and/or distressing recollections, dreams, and flashbacks. Patients may also have a numbing of general responsiveness or symptoms of hyperarousal. These symptoms must persist for longer than one month.

Mood

Depression is both a symptom and a disorder, marked by feelings of sadness, guilt, hopelessness, and apathy. It is quite common, as evidenced by its high lifetime prevalence (16.6% according to Kessler et al. [1]). The stereotypical impression of the elderly is that they may be more prone to depression because of loneliness or difficult life changes, but depression is not a normal part of aging and is often a treatable disorder [6]. Studies show that older people are satisfied with their lives and less likely to experience depression than younger adults [7]. However, depression is still a serious problem in the elderly, with consequences both for the individual and for society [8]. It is an important public health issue that leads to increased morbidity and disability [9]. Depression can also be more difficult to diagnose in the older population because some of its symptoms can be mistaken for normal physiologic changes of aging or side effects of medicines more commonly taken in later life.

Key depressive disorders in older adults include the following:

- Major depressive disorder requires the presence of at least one major depressive episode, which is defined by five or more specified depressive symptoms that occur in a single two-week period, one of which must be depressed mood or anhedonia. The symptoms are present a minimum of most of the day on most days and result in clinically significant impairment of the patient's social or work life. Depressive symptoms include depressed mood, anhedonia, loss of interest, change in sleep patterns and/or appetite, guilt, psychomotor retardation, inability to concentrate, decreased energy, and thoughts of suicide. In older adults, depression can present in an atypical fashion. They often complain of more somatic symptoms; and apathy, irritability, and social withdrawal are more common complaints than depressed mood [7]. In fact, elderly patients often deny being depressed. A key feature of major depression in aging is an unrelenting, ruminative focus on a self-perceived cognitive impairment with or without supporting evidence. Major depressive episodes can present with psychosis, in older adults often associated with delirium and/or dementia but also possibly related to sensory impairments (visual or auditory). Patients with both dementia and a mood disorder may present with irritability or elevated mood. As in any patient with major depressive disorder, it is important to rule out somatic causes of the mood disorder. It should also be noted that the highest rate of suicide in the USA is in individuals in the age range of 65 and above.
- Bipolar disorder is a different type of depression that can feature manic, mixed, hypomanic, and depressive episodes, depending on the subtype. A manic

episode is defined by an abnormally elevated, expansive, or irritable mood that lasts continually for at least one week. Symptoms include but are not limited to excessive or pressured speech, a decreased need for sleep, grandiosity, increased activity, racing thoughts, flight of ideas, distractibility, and impulsivity. Ten percent of patients with bipolar disorder develop first-onset mania after age 50. In older adults, this is often because of medical or neurologic disease or the use of steroid medications.

- Dysthymic disorder is another type of mood disorder, characterized by chronic depressive symptoms that are less severe than those of major depression but that last longer.

Adjustment

Adjustment disorders with anxiety or depressive symptoms, commonly diagnosed by specialists following psychosocial stressors, do not meet the criteria for a major depressive episode. There is still much to be learned about the significance of these syndromes, as well as effective treatment [10]. It seems logical that adjustment disorders would be more common in later life because the risk of stressful events and loss of life become greater; however, it appears that many older persons' expectations of major stressors and loss change, leading to a lower prevalence of adjustment disorders with aging. In addition, coping mechanisms develop over the course of a lifetime that can lower the risk of adjustment disorders. Bereavement is a diagnosis that features depressive symptoms. It is considered normal grieving when it occurs within two months of the death of a loved one.

Prevalence

Struggling with a psychiatric disorder at some point over the course of one's lifetime is quite common. Anxiety and mood disorders, in particular, have a high rate overall that decreases with aging. Symptoms of anxiety and depression often occur together and in older adults are commonly subthreshold (do not qualify for a full diagnosis).

Lifetime Prevalence and Age of Onset of Psychiatric Diagnoses

The lifetime prevalence of any *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* [11] diagnosis across all ages is 46.4% [1]. In particular, the lifetime prevalence of anxiety and mood disorders is 28.8 and 20.8%, respectively [1]. The age of onset of anxiety disorders is much earlier (age 11 years) than that of mood disorders (age 30 years), and mood disorders have a wider range

of age at onset than other classes of psychiatric disorders [1]. There has long been an association between symptoms of anxiety and depression [12], but it is still uncertain whether these are distinct entities that may co-occur or whether they are points along the same continuum. Mixed anxiety-depressive disorder (MADD) is a provisional diagnosis in the *DSM-IV* and International Statistical Classification of Diseases and Related Health Problems, Tenth Revision that describes co-occurring, subsyndromal anxiety, and depressive symptoms. A study done in Great Britain showed that, in patients with MADD, 47.9% had both specific depression and anxiety symptoms; and 98.9% had nonspecific somatic symptoms, fatigue, concentration problems, sleep problems, irritability, or worry [13]. Some critics of the provisional diagnosis point out that, although MADD is associated with impaired functioning, the disorder as described has low diagnostic stability over time; and its incidence may be dependent on the defining criteria [14]. However, studies have concluded that patients with the provisional diagnosis of MADD have more severe and chronic pathology than patients with depression or anxiety only, resulting in greater vulnerability [4, 15].

Prevalence of Mood and Anxiety Disorders in Older Adults

National. Although the prevalence of mood and anxiety disorders declines with increasing age, they are still common and require preventive considerations, as well as intervention [7]. Special considerations in the elderly include the prevalence of chronic illness and the effect that medical comorbidities have on psychiatric complaints and vice versa. According to data from the National Comorbidity Survey Replication, the 12-month prevalence rates of any mood disorder and any anxiety disorder in adults ages 55 and older were 4.9 and 11.6%, respectively. Comorbid mood and anxiety disorders have a prevalence of 2.8% in older adults. In general, rates of both mood and anxiety disorders decrease steadily with age, except in the oldest old (age 85 or older); but this age group is the least available for study [7], and selective nonresponse of the most frail is an issue in community-based studies [8]. The most common anxiety disorder in older adults is specific phobia, followed by social phobia, PTSD, GAD, panic disorder, and agoraphobia. Being married or cohabiting is protective against mood and anxiety disorders, and low education level is a risk factor for anxiety in aging. There is a significantly higher risk of anxiety in women [7, 16]. There are no significant changes in prevalence of disorders according to race or geographic location [7]. Some considerations should be kept in mind when reflecting on these data, including possible underreporting of psychiatric illness in the aging population. Potential causes of this include embarrassment associated with the stigma of mental health problems, difficulty recalling symptoms or associating those symptoms with psychological distress, and the underrepresentation of the homeless, institutionalized, and non-English-speaking older-adult populations [7].

Worldwide. Results of a study investigating the prevalence of anxiety among older adults in low- and middle-income countries were comparable to the rates in

high-income countries, with the exception of China, which had a remarkably low prevalence of anxiety. This finding may be because of a cultural stigma associated with mental illness. The highest prevalence of anxiety among older adults was found in Latin America. This study confirmed that the risk factors for anxiety in older adults in the USA parallel those in the other countries surveyed. The most important factors were gender, socioeconomic status, and comorbid physical illnesses. Significant levels of comorbid depression and anxiety were reported, with more than one fifth of the anxiety disorders featuring comorbid depression in all countries surveyed [17].

Prevalence of Depressive and Anxious Symptoms in Older Adults

Although the prevalence of diagnosable mood and anxiety disorders decreases in later life, the elderly population still often experiences subclinical symptoms of anxiety and depression [5]. According to the US Center for Disease Control's (CDC) report, *The State of Mental Health and Aging in America*, 9.2% of US adults age 50 or older and 6.5% of US adults age 65 or older reported "frequent mental distress," defined as 14 or more days of poor mental health over the past 30-day period. Current depression was reported by 7.7% of adults age 50 or older, with 15.7% reporting a lifetime diagnosis of depression [18].

Pathophysiology

Although anxiety and depressive symptoms may either co-occur or may be distinct, their biological causes are closely linked. Evidence shows that abnormalities of both the serotonin and norepinephrine neurotransmitter systems are present in anxiety and depression [19].

Special Considerations for Older Adults

There are some important concepts to keep in mind when working with geriatric patients. In the geriatric population, attention should focus on level of functioning and quality of life as well as safety. The physician should take a comprehensive medical history and review all medications to rule out any alternative treatments for psychiatric complaints. Care should also be taken to evaluate cognitive functioning and frontal-lobe impairment. With regard to psychiatric complaints, the patient is often not the complainant, so it is important to find collateral sources of information, such as family members or caregivers. Because of a decreased functional

reserve, when illness strikes the older adult, he or she may be less equipped than the younger adult to bounce back and be more vulnerable to quick deterioration, loss of functioning and difficulty with activities of daily living. Care must be taken to recognize the bidirectional association between medical illness and psychiatric complaints that negatively affects treatment of both and results in a poor prognosis.

With the increasing number of medical problems and chronic disease in the elderly, some physicians expect symptoms of anxiety and/or depression as a natural consequence. The effect of medical comorbidities and chronic pain on anxiety and depression is significant, and the reverse is true as well. Anxiety and depressive symptoms can adversely affect the course and complicate the treatment of chronic medical diseases [6]. For example, in some chronic respiratory diseases, particularly chronic obstructive pulmonary disorder, the presence of anxiety and depression can compound the physical and emotional effects of breathing disorders [20]. This leads to the question, what level of anxiety and depressive symptoms is normal in adults; and how is the treatment of one intertwined in the other? Refer to Chaps. 10, 11, and 17 for further discussion.

Biopsychosocial Model

The World Health Organization defines *health* as "… a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" [21]. This definition sparked extensive discussion and theories on how to approach health care with a comprehensive, multifactorial viewpoint. Here we will explore the biopsychosocial model and the transformation of thought to a subsequent conceptual model that refocused attention on chronic illness and its association with psychiatric problems.

History of the Model

The theory behind the biopsychosocial model, a concept described by Dr. George Engel in a 1977 article in *Science* [22], was not new at that time by any means. Physicians have a long history of incorporating patients' background and attitudes toward disease in their diagnosis and clinical decision making. In fact, this type of holistic approach to healing dates all the way back to Hippocrates. At its heart, the biopsychosocial model implies that a person's biologic tissue changes his/her personal history, and his/her social circumstances all contribute to illness. The notion of "treating sick people and not diseases" [23] was emphasized again and again over time. It is notable that, in Engel's description of the model, he added the role of the healthcare system as a social factor. At the time of the published description of the model, the so-called biomedical model of disease was falling out of favor, as people suspected the powers of pharmacologic tools focused

solely on altering molecules had a limited ability to cure disease. In fact, people may have been losing faith in the healthcare system itself. Emphasis in Engel's article was placed on the interpretation of the terms *sick* and *well*, and the idea that more factors than just biology played a role in wellness, especially in the way patients viewed their own disease. However, Engel did not diminish the importance of the biomedical in his description. His training background as an internist and the passion for psychoanalysis he later developed seem to have heavily influenced his desire to link somatic illness with life situation and personal development [24].

Modernization and Application to Psychiatric Symptoms and Disorders

In 2003, an article was published that presented a new conceptual model by Wayne Katon. Despite having many similarities to the biopsychosocial model, this model was updated to become more biologically focused in presenting the reciprocal cause-and-effect pattern of chronic diseases on depressive and anxiety disorders and vice versa. It was based on a number of studies showing a link between chronic disease and mental disorders. Patients with any chronic medical condition are more likely than those without to experience depression [25], and the most common reason for new onset of major depression is the diagnosis of either the patient or his or her spouse with a life-threatening illness [26]. Because of the association between mental disorders and poor physical health, psychiatric assessment becomes all the more important in the elderly population [7]. Katon investigated the link between depressive and anxiety symptoms and disorders in patients with various neurologic diseases, diabetes, heart disease, and HIV and realized that depression plays a significant role in the development of some diseases. Depression can also develop as a result of the psychological reaction to disease. There is a causative role between depression and complications related to disease. Finally, depression is known to be a side effect of many medications and treatments. Katon also pointed out that chronic medical illness has a pathophysiologic effect on brain chemistry and function [27].

The cornerstone of Katon's conceptual model is that depression and anxiety affect behavioral risks for chronic disease, which, in turn, lead to chronic disease. Both the disease itself and the depression and anxiety lead to worsening self-care, thereby leading to myriad consequences of chronic illness, like worsened quality of life, functional impairment, and biologic changes and symptoms. The model also highlights the effect on chronic disease of biopsychosocial factors, such as genetic vulnerability, childhood adversity, adverse life events, and maladaptive attachment.

All these factors must be considered in the diagnosis and treatment of comorbid medical disease and mental illness. There is no population to which this model is more applicable than older adults, with their continually increasing rates of comorbid chronic disease. The following discussion of successful aging precedes a further investigation into changes in the above conceptual model with aging.

Aging

This section discusses the concept of successful aging and provides a brief overview of the global impacts of an aging population. Depression and anxiety are discussed in the context of the biopsychosocial model and the evolution of risk factors for the older population.

Successful Aging

There has long been controversy in the USA surrounding the traditionally negative view of aging and the elderly. Since Robert Butler [28] first coined the term *ageism* in his award-winning book, *Why Survive? Being Old in America*, in 1969, stereotypes of the elderly have run rampant; and scholars and laypeople alike have asked how we can age successfully. In 1998 Doctors Rowe and Kahn published an article called "Successful Aging" addressing these issues. Attention and research are becoming more focused on identifying the factors involved in successful aging and on decreasing related morbidity and mortality [29]. The multidimensional approach involves three main categories: avoidance of disability and disease, maintenance of daily cognitive and physical functioning, and continued social and productive involvement [30].

In the past, the idea that the elderly population represented a burden on society created a stigma associated with aging. Emphasis is now being placed on the positive aspects of aging. A study of a two-factor model of success in aging looked at objective factors (measured by lack of disease, lack of pain, and functional ability) and subjective factors and showed that the two are not independent [31]. According to this model, people can feel they are aging successfully, despite objective factors such as chronic disease and decreased functioning [29]. Frailty as perceived by outsiders is generally not in line with the self-perception of the elderly. As discussed above, the prevalence of depression and anxiety in the aging population is lower than it is in younger adults. Of course, the consideration of other aspects of aging, such as health and disease, and nursing and welfare issues and their effects on industry and the economy, is integral to a balanced assessment [32].

Global Aging Population

Globally, life expectancies are increasing as a result of improved nutrition, sanitation, medical advances, health care, and economic well-being. The ratio of people in the work force to those who are retired has already and will continue to decrease dramatically [33]. This could lead to drastic economic and social downturns if we do not make changes to allow successful aging. An important impact of the aging

population is an increasing patient load with multiple chronic diseases and, therefore, an increasing number of patients with symptoms of depression and anxiety secondary to their disease processes. Other major risk factors are discussed below.

Depression/Anxiety in Aging: Changes to the Model

Changes to the model have occurred because many of the risk factors for anxiety and depression, as well as the expectations regarding life events change with age.

Risk Factors

The risk profiles for depression and anxiety change in older adults, as exposure to these risk factors and their corresponding impacts change with age. Many of these risk factors simultaneously represent major barriers to successful aging, as described above. Studies show a considerable amount of overlap between the risk factors that influence anxiety and depression [8].

Biologic

Biologic factors include the following:

- Deteriorating physical health and chronic medical illness

  A recurring theme in this text, the link between deteriorating physical health and depression and anxiety, cannot be overemphasized in the aging population [25, 26, 34]. Chronic illness, especially multiple comorbid illnesses, can result in both anxiety and a feeling of hopelessness. Respiratory disease, in particular, is further discussed throughout this text.

- Cognitive decline

  Older adults with dementia or other mild cognitive impairment experience neuropsychiatric symptoms significantly more often than those without cognitive impairment [35]. These symptoms may include agitation, apathy, depression, delusions, and hallucinations. The negative association between cognitive performance and depressive symptoms was even true in the subclinical range of symptoms [36]. Additionally, evidence shows that cognitively impaired older adults have a greater prevalence of anxiety symptoms than those without cognitive deficits [37]. Cognitive impairment can also have detrimental effects on successful treatment. For example, pharmacotherapy adherence requires that medication be taken on a regular basis, at the correct dose, in an appropriate manner, which requires intact executive functioning and memory [38]. There are

many types of aids available that can help mitigate this aspect of the risk. Both cognitive impairment and symptoms of anxiety and depression are associated with a variety of problems, including caregiver distress and greater supervision time; functional limitations; and, in some cases, earlier institutionalization [35].

- Personal and family history of anxiety and depression

  A personal and/or family history of mental illness is traditionally a major risk factor considered in examination and diagnosis of younger adults. However, these factors become less important in the risk profiles in older adults, particularly those whose depression or anxiety first appears late in life. This may be because of the most vulnerable elderly selectively leaving the population pool [5, 39].

Psychological

Psychological factors include coping with loss of functioning, changes in role function, and end-of-life considerations.

- Coping with loss of functioning

  Along with the biologic changes in aging, such as chronic medical conditions and impaired cognition, come changes in ability to function on a day-to-day basis. As patients grow older, they themselves and/or their partners or companions may not be able to do some of the things they used to enjoy. The psychological aspect of this is in how persons cope with this loss of functioning and, sometimes, the loss of autonomy. The risk for depression and anxiety lies in an inability to accept these changes, which can become an inward focus of negativity and disappointment.

- Changes in role function

  A common problem that older adults experience is difficulty adapting to a change in their social role. For example, some find that, after a lifetime of work, it can be difficult to transition to retirement. Some people do not know what to do with their extra time; and, more often, the conversion from "breadwinner" can be difficult. Additionally, many people attribute a major part of their identities to their work. Without it, they may leave behind a large portion of their social circle and can feel isolated and lost.

- End-of-life considerations

  Older people have variable courses of decline that are different than those of younger adults with terminal diseases, for example. Feelings of fear and anxiety about death are less common in older adults, although they still occur. Many older people do not want to endure pain or prolongation of their declines.

Social

Social factors include a diminishing social network/loneliness and financial concerns.

- Diminishing social network/loneliness

  As people age, the loss of social connections is typical. The social network associated with one's job is diminished or lost with retirement. As physical health problems grow, the ability to keep up with friends or family members may fade as a result of the inability to drive or physically move around well. Confinement to a wheelchair or dependence on a caregiver can severely limit social interactions outside the home. The loss of peers occurs frequently with aging, adding to loneliness in some. This social loss can cause some older adults to realize the brevity of their remaining lives and may lead to depressive or anxiety symptoms [40].

- Financial

  There are three major categories of financial concern for the aging population. The first concerns fixed incomes: often, older adults have to adjust to a more limited income than before, one solely from retirement, social security, or pension plans. Physical or psychosocial problems may prevent older adults from working; and sometimes this limited income can become a major burden, especially if they have not encountered it before. Secondly, healthcare costs skyrocket with aging. Costs for other necessities do not necessarily decrease, and the increasing cost of health care with aging may take some people by surprise. Finally, financial abuse of the elderly is a common problem; and, often, they may not have the financial resources to recover from it. Isolation, loss, and loneliness can impact judgment and leave the elderly vulnerable to this abuse.

Further study of these biologic, psychological, and social risk factors, some of which are inevitable as one ages, is crucial to promote understanding and management of the issues that impede successful aging.

Change in Expectations with Age

Some risk factors change with age as people's expectations of life events change. This may shed some light on the evidence that emotional well-being improves from early to late adulthood [41]. The understanding that major life events occur on a loosely predetermined timeline can result in changes in ease of adaptation to these events for better or worse. For example, the death of a spouse, for a younger adult, is often unexpected, leading to greater risk of psychiatric manifestations than for an older adult. In later life, the death of a spouse in some cases may be expected, which

can alleviate the impact [5, 8]. In addition, aging is associated with a growing preference for positive over negative information [41].

Treatment

This section provides a brief overview of the types of treatment available for mood and anxiety disorders, along with some principles to follow in treating an aging population. For more detail on nonpharmacological and pharmacological treatments of depression and anxiety in chronic respiratory disorders, refer to Chaps. 10 and 11, respectively. Chapter 12 provides a care-based approach to management of psychiatric disorders in chronic respiratory disease.

Types

Types of treatment include pharmacotherapy, electroconvulsive therapy (ECT), psychotherapy and cognitive behavioral therapy (CBT), and education.

Pharmacotherapy

Older adults are not well represented in clinical pharmaceutical trials. They are often excluded for their age, comorbidities, or both [42]. This leaves physicians to extrapolate from trials with younger adults, resulting in uncertain outcomes [43]. Additional problems related to pharmaceutical treatment of anxiety and depressive symptoms in geriatric patients are their increased sensitivity to side effects, such as sedation, orthostasis, extrapyramidal symptoms, increased fall risk, disinhibition, paradoxical agitation, and the syndrome of inappropriate antidiuretic hormone secretion [44]. Comorbid disease and behaviors can also alter effectiveness of drugs. Nonetheless, many pharmacologic treatments have been shown to positively affect outcomes [45].

- Antidepressants may be used to treat both depression and anxiety. No one antidepressant has been shown to be more effective than another. Medication selection includes consideration of side effects, drug–drug interactions, and cost, among other factors. In the geriatric population, special attention must be paid to drug–drug interactions, as well as the presence of poor sleep, weight loss, and comorbid anxiety with depression. Psychostimulants may be used in depressed older adults if an urgent response is needed.
- Benzodiazepines are an effective treatment for anxiety and are commonly prescribed; however, benzodiazepine use in older adults is associated with serious adverse effects, including increased risk of falls and accidents, heightened risk of

cognitive impairment, and development of tolerance and addiction [3, 43]. Additionally, benzodiazepines are more appropriate for treatment of acute anxiety; while, in the elderly, anxiety symptoms are more often chronic and may be milder, making this choice of treatment inappropriate in many cases.

- ECT is effective in older adults for psychotic depression, refractory depression, and mania. Extreme care should be taken to rule out medical causes of psychiatric symptoms before treating with ECT.
- Behavioral therapy and psychotherapy are important augmentations to pharmacologic treatment. CBT is especially effective in treating anxiety disorders. It should be noted that older adults with cognitive or sensory impairments are less likely to benefit from psychotherapeutic interventions [43].
- Education is a key part of treatment of depression and anxiety in older adults, not only of the patients themselves but also because of their caregivers and the public. This can be used to decrease stigma and other modifiable barriers to mental health issues [38]. Electronic tools are an up-and-coming means of detecting problems and providing education.

Principles of Treatment in Aging Literature

Principles that should be taken into consideration in treating anxiety/depression in older adults include the following:

- "Start low; go slow." A change in drug clearance can increase sensitivity to pharmaceuticals in the elderly, so it is important to begin with a lower than recommended dose and titrate up slowly until the desired effects are seen. All drugs should be monitored for toxicity.
- Quality of life. Traditionally, physicians have focused on the diagnosis and treatment of disease. This is no doubt of utmost importance, but the focus should change with altered circumstances. In the aging population, especially the oldest old, the highest emphasis should no longer be placed on disease itself but rather on improved quality of life and avoidance of suffering. This is an important principle that separates geriatric medicine from general medicine and holds true in psychiatric treatment as well. Interventions should be tailored to the individual and should center on optimizing quality of life and maximizing functioning [38].
- Shortfalls of treatment. The rate of nonadherence to treatment in the older population is quite high [46]. It follows that a need for more intensive follow-up is required for these patients than for younger patients. However, even with appropriate evidence-based treatment, the negative consequences of anxiety and depression in older adults may not always be avoided. One study showed that only 50% of the burden of anxiety disorders and 35% of the years lived with a mood disorder could be averted [5, 47]. This supports the importance of screening in older adults, especially those at high risk, and early diagnosis of depression and anxiety.

Treatment Preferences in Elderly Versus Younger Patients

Older patients may themselves be the greatest hindrance to treatment of mental health problems. Many older adults have a deep-seated belief in self-reliance. Compared with younger adults, they are less likely to admit mental health problems in either the past or present and are less likely to desire help with any current emotional problems [48]. Adults age 65 and older have the lowest self-perceived need for mental health services of any age group [49]. Although they are as open to physical fitness programs as younger adults, the older population is less amenable than younger adults to the idea of attending counseling or stress-management programs [48]. Often older and younger adults have similar outcomes of treatment for psychiatric problems, but the efficacy of different types of interventions and the tolerability of medication side effects may be different in these populations [43].

Ethnicity may also play a role in resistance to treatment in older adults. Both cultural and racial backgrounds affect attitudes toward mental illness, its cause, and its treatment [50]. Minority elders are less willing than nonminority patients to participate in psychotherapy [51].

Finally, there is a far more pervasive set of preconceptions about pharmacotherapy for mental illness in the old versus young age groups. Some older adults suspect a lack of efficacy or fear adverse effects or addiction [52]. Younger adults have more familiarity with pharmacotherapy, resulting in higher acceptance and adherence to treatment.

Access to and Use of Mental Health Care in the Elderly Population

Two factors affect the delivery of mental health care to older patients: the fact that primary care is the main arena is which older patients receive both medical and mental health care and the existence of stigma associated with treatment for issues of mental health.

Primary Care Versus Mental Health Care

Both anxiety and depression, whether warranting diagnosis or subthreshold, are underrecognized and undertreated in primary care [5, 53, 54]. One explanation for this is the common somatization of symptoms in older adults [5, 53]. Depressed patients, independent of age, are more likely to look to primary care physicians for somatic symptoms than they are to self-identify mental problems and present to mental health professionals [55]. Thus, in the elderly population, patients are far more likely to be treated for symptoms of anxiety and depression in primary care

than in a mental health setting. Failure to recognize psychiatric symptoms in primary care leads to a lack of appropriate treatment and poor outcomes [53].

Intuitively, one would expect the severity of psychiatric symptoms to have a direct relationship to the frequency of detection of mental illness. The more severe the symptoms, the more likely they will be recognized in a primary care setting [55]. On the other hand, because older adults more often exhibit less severe subthreshold anxiety and depressive symptoms, there is a tendency to overlook these problems. This is worrisome because late detection of anxiety and depression is associated with poor prognoses.

One factor that seems to raise detection of mental health issues is comorbid medical illness [55]. The higher frequency of doctors' visits may allow a better rate of detection.

There also exists a particular problem with detection of mental health problems among minority populations. Primary care providers are less apt to recognize psychiatric symptoms in African-American and Hispanic patients; in addition, these minorities are much less likely to seek mental health care on their own than non-minority populations [50].

Compared with mood disorders, anxiety disorders result in far fewer referrals to mental healthcare professionals [5]. In the context of the earlier age of onset of most anxiety disorders, one must consider the possibility that both patients and physicians attribute anxiety and avoidance symptoms to personality traits rather than a psychiatric disorder [3]. Additionally, there is a general lack of expertise in geriatric care, leading to the failure to incorporate evidence-based practice into treatment of mental illness in the elderly [43].

Stigma of Mental Health Care

The stigma associated with mental illness remains a major barrier to treatment in older adults [9]. The stigma comes from both external sources (the perceived negative beliefs, attitudes and conceptions about mental illness of the public), as well as internalized negative attitudes about one's own mental problems. Internalized stigma leads to devaluation, shame, and social withdrawal [56]. This stigma, regardless of its origin, leads to a sharp decrease in treatment-seeking behavior [9]. Older adults with psychiatric problems endorse feelings of both public and internalized stigma that lead to a strong reluctance to seek psychiatric care [9]. As earlier discussed, this stigma plays a major role in creating attitudes that contribute to a decreased utilization of dedicated mental health care. In turn, many older adults with psychiatric distress are treated by their primary care practitioners, or not at all. This psychosocial issue is a problem across the spectrum of mental health treatment [9]. However, it stands to reason that, as younger generations become the older population, the stigma associated with psychiatric problems will lessen. Perhaps morbidity and impairment resulting from mental illness will lessen as well, thus relieving the negative effect it has on chronic disease in the elderly.

Underreporting of Disease

A direct effect of the stigma of mental illness perceived by the older population is underreporting of both psychiatric symptoms and disorders. Many older people are too embarrassed to admit to these problems, both in their primary care physicians' offices as well as in surveys. This results in a lack of diagnosis and an associated failure to treat, as well as underreporting and underfunding of mental health issues [7].

Caregivers' Attitudes

The attitudes of caregivers of the elderly regarding mental health are important to consider, as caregivers have an increasing influence on decisions impacting patients' care over time. The effect of the stigma of mental illness on caregivers should be assessed, and the caregiver should be included in the treatment plan where possible to promote patient compliance and adherence [38]. This directs our attention once again to the societal issue of stigma of mental health issues and the importance of addressing this problem, which has a large and broad impact. Assessing and addressing the source, as well as the resultant problems of this stigma, could potentially diminish its negative effect on the elderly.

Consequences

Anxiety and depression in the elderly can have a major impact on the family. Caregivers may succumb to "compassion fatigue" in which their relationship, based on empathy, results in a state of major psychological distress that progresses to social, spiritual, and physical exhaustion [57]. This may result in earlier institutionalization of the elder. Other consequences include family financial trouble, societal economic problems, and a major psychological effect on other members of the family and social circle in addition to the caregiver.

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Chapter 3
Diagnostic Tools for Anxiety and Depression

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Introduction

Depression and anxiety are common in patients with COPD. The prevalence of depression in patients with COPD ranges between 8 to 80% and 6 to 74% for anxiety symptoms [1, 2]. This is similar to patients with chronic heart failure (CHF) estimated between 10 and 60% for depression and 11–45% for anxiety [1]. The exact mechanism and factors that contribute to the elevated level of anxiety and depression in patients with COPD are unknown. They are most likely to be multi-factorial. Moderate-to-severe COPD patients are most likely to experience severe limitation in their daily activities due to loss of energy and severe breathlessness, higher frequency of hospitalisations due to acute exacerbations, and being housebound due to the progressive disabling nature of the condition [1, 2]. Indeed, these factors may contribute to additional burden and may dislocate coping mechanisms when they are compounded with mood disorders in patients with COPD.

The diagnoses of both major depressive and anxiety symptoms are complicated in patients with COPD due to overlap of symptoms due to physical ill health. In addition, some of the difficulties may include lack of knowledge or understanding of depression by patient and carers; a fear of rejection by the society; the tendency to avoid psychiatric care because of stigma; and the reduction of social and work contacts which makes depression a relatively hidden disorder [3–5]. Indeed, psychiatric assessment in old age may be more complicated, for example, the physician may be unable to extract detailed history because of cognitive impairment, denial or reluctance by the patient.

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There is increased recognition that anxiety and depression have considerable impact on patients' health status and healthcare utilisation. However, there are no disease-specific tools that have been developed and validated to asses these symptoms in patients with COPD. Currently, a number of screening tools have been used in research and in clinical practice to assess anxiety and depressive symptoms. Therefore, it is important for clinicians and researchers to have an in-depth understanding of their strengths and limitations of these tools. This chapter reviews the most commonly used screening tools for anxiety and depressive symptoms in patients with COPD, primarily developed and employed to assess these symptoms for patients with or without chronic conditions. Furthermore, the review provides clinicians with practical tips when to use (clinical diagnostic tools) or refer patients to psychologist/psychiatrist for further assessment. It will also provide some guidance areas for future research and outcome measures that have been used in clinical trials.

What Are the Potential Difficulties Associated with Detection?

If mood and anxiety disorders are so common, why are they often undiagnosed and untreated in COPD? First, screening tools for depression or anxiety symptoms are not routinely used in clinical practice. Second, depressive and anxiety symptoms in patients with COPD might be masked by physical symptoms such as decrease in exercise tolerance, breathlessness, fatigue and increased dependency in daily activities. Furthermore, in patients with COPD, poor health, bouts of chest infection and frequent episodes of hospital admission are so common as to be almost accepted scenario for many patients. In this context, patients may not disclose depressive or anxiety symptoms unless they are specifically asked [6]. Other contributing factors might be that not all physicians are confident enough to pursue psychiatric assessment and patients may fear approaching their physicians because of the stigma of mental illness. Lack of public awareness fuels this continued stigma [5] and depression itself is associated with its own specific stigma [7] and fear of anxiety during social interaction.

Screening Tools for Anxiety and Depression

The purpose of a screening tool is to identify those patients who are in need of further psychiatric examination. Identifying high numbers of false positives is costly, both financially, and in terms of wasted time for the clinician and the patient. A scale that can efficiently screen patients for anxiety and depression is

characterised by a high sensitivity, which ensures that all individuals with an anxiety disorder are identified [8].

Self-report rating scales are designed to be measurement instruments that quantify patients' subjective experiences and aid the clinician in identifying, quantifying and tracking changes in these important but not directly observable variables [9]. Self-report scales typically fall into two groups: screening scales and symptom-rating scales. Screening scales are designed to identify the presence or absence of a specific disorder, such as a personality disorder, and provide a dichotomous outcome (i.e. case or non-case). In comparison, symptom-rating scales are designed to quantify the severity of symptoms. This may involve measuring the severity of symptoms in a prediagnosed disorder, or monitoring of subclinical symptoms [9]. Although rating scales quantify symptom severity, many also report cut-off scores that can be used to indicate possible clinical disorders in a dichotomous fashion.

Self-report scales have become increasingly popular since the 1940s due to a growing need for reliable and valid outcome measures for both research and clinical practice. In addition, Kessler et al. suggest [10] that there are a number of important practical benefits to self-report scales. First, they are relatively inexpensive to develop and distribute. Second, the continuous measurement approach is better suited to the understanding of diverse symptoms than a dichotomous clinician judgement. Third, the psychometric properties of self-report scales are easier to record than clinician judgement.

Self-report scales fulfil, if developed appropriately, many of the criteria that are required from an outcome measure. For example, a survey of Canadian clinicians found high levels of agreement that outcome measures used in clinical practice should have the following characteristics: brevity, simplicity, ease of scoring, reliability, validity and sensitivity to change [11].

Although self-report scales have a number of strengths that make them suitable for both clinical and research settings, there are a number of factors which influence their effectiveness and application. These fall under two main categories: response distortions and psychometric properties. Response distortions refer to response styles (such as acquiescence bias, extreme and central tendency responding) and response sets (such as social desirable responding), whereas psychometric properties refer principally to reliability and validity.

Assessment and Diagnostic Tools

The use of psychological screening tools for assessment anxiety and depression in older people with co-morbid physical illness [12] may allow healthcare professionals:

- to increase early detection of depression and anxiety;
- to plan treatment action in those identified with symptoms;

- to monitor changes over time in the patient's condition;
- to evaluate the response of the older person after intervention;
- to tailor individual's patient needs in clinical and rehabilitation programme;
- to provide appropriate support to family and care givers;
- to reduce the risk overlooking important patients symptoms.

In this regard, early detection of depression and anxiety play an important role in the management of patients with COPD. The commonly employed screening tools for depression and anxiety in patients with COPD are listed in Tables 3.1 and 3.2. When an individual patient responds positive (suffering with depression and anxiety using a screening tool), he/she should be assessed further for the cause(s) of current depressive or anxiety episode by the healthcare professionals (e.g. general physician). Therefore, thorough physical examination will help to focus on the patient's problems and to devise appropriate (individually tailored evidence-based treatment) including referring patients for further assessment.

Table 3.1 Depression screening scales

Scale	Number of items	Mode of administration	Duration (min)	Application	Timeframe (days)	Response options	Score range
BDI	21	Self or interviewer	5	Screening tool	21	Likert 0–3	0–63
HADS (depression)	7	Self	2–5	Screening tool	7	Likert 0–3	0–21
BASDEC	19	Interviewer using deck of cards	4	Screening tool	14	Yes or No. (1, 0) or I do not know (0.5)	0–21
CES-D	20	Self or interviewer	5–10	Screening	7	Likert 0–3	0–60

BDI Beck Depression Inventory; *HAD* (depression); *BASDEC* Brief Assessment Depression Examination Cards; *CES-D* Centre for Epidemiologic Studies Depression Scale

Table 3.2 Anxiety screening scales

Scale	Number of items	Mode of administration	Duration (min)	Application	Timeframe	Response options	Score range
BAI	21	Self or interviewer	5	Screening tool	21 days	Likert (0–3)	0–63
HADS (anxiety)	7	Self	2–5	Screening tool	7 days	Likert (0–3)	0–21
STAI (trait anxiety)	20	Self	10	Screening tool	"Right now"	Likert (1–4)	20–80
GAI	20	Self or interviewer	5–10	Screening	7 days	Disagree or agree (0–1)	0–20
AIR	10	Self	3	Screening	14 days	Likert (0–3)	0–30

BAI Beck Anxiety Inventory; *GAI* Geriatric Anxiety Inventory; *HADS* Hospital Anxiety and Depression Scale; *STAI* State-Trait Anxiety Inventory; *AIR* Anxiety Inventory Respiratory Disease

Depression

Diagnostic Criteria for Major Depression

Depressive episode is a syndrome that includes depressed mood, anhedonia (loss of interest or pleasure) and fatigue that is present for a period of at least 2 weeks.

Diagnosis is made by a structured interview using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association [13]) criteria. Major depressive episode may include: five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day.
2. Markedly diminished interest or pleasure in all or most activities.
3. Weight changes more than 5% of body weight in one month, including weight loss without dieting, and a decrease or increase in appetite.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor retardation or agitation.
6. Loss of energy, or fatigue.
7. Feelings of worthlessness or guilt.
8. Inability to concentrate or make decisions.
9. Recurrent thoughts of death, or suicidal ideas or suicide attempt.

It takes about 30 min to administer the scale and the gold standard for the diagnosis of bout major and minor depressive symptoms. However, the downside of the scale is time-consuming and requires special training to administer the scale.

Geriatric Mental State Schedule (GMS)

The Geriatric Mental State Schedule [14] is a well validated scale used to diagnose clinical depression and anxiety in elderly people including those with chronic diseases. It is one of the most widely used and respected instruments for measuring a wide range of psychopathology in elderly people. It is based on the Present State Examination [15] and the Psychiatric State Schedule [16]. It has been adopted for use on laptop computer via software which generates a diagnosis, the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) [17], and is replicable (when used in hospital and community samples) against psychiatrists' diagnosis [17]. Its internal validity and reliability have been established [18], and it has been used in a cross-national setting [19]. The GMS delivers a diagnosis using a hierarchy which corresponds to approaches to diagnosis by a trained psychiatrist. There are 5 levels of severity generated by GMS for 5 diagnostic groups and a level of 3 or above corresponds to a "case". Thus, level 3 and above in the depression

group is diagnostic of clinical depression, and level 3 or above in the anxiety group diagnostic of clinical anxiety. It requires a trained member of staff for the interview and takes about 40 min to administer.

Montgomery–Asberg Depression Rating Scale (MADRS)

The MADRS assesses severity of clinical depression [20], has been validated in medically ill elderly patients and is widely used in the context of other chronic diseases. It has ten items scored compositely which result in a maximum total score of 60. It classifies severity of depression into four categories: normal, i.e. not depressed (0–6); mild (7–18); moderate (19–34); and severe (>35) [21]. Low scores imply mild depression and high scores correspond to severe depression. Subjects rate their responses using a Likert 7-point category scale, for example, 0 = "no sadness", 6 = "miserable all the time". The MADRS has performed better in identifying responders and non-responders to antidepressant drug therapy than the Hamilton Depression Rating Scale (HDRS) [20]. A study by Hammond [22] identified the inappropriateness of HDRS (because of very low internal consistency) in determining severity of depression in the physically ill-depressed elderly patients but recommended the MADRS as a preferable choice. A study by Yohannes et al. [23] using the MADRS scale in patients with COPD identified the severity of depression 17 (30%) were mildly depressed (MADRS score 7–19), 39 (68%) were moderately depressed (MADRS score 20–34) and 1 (2%) was severely depressed (MADRS score 35–60). It requires a trained person to administer the scale.

The Hamilton Depression Rating Scale (HDRS)

The HDRS measures the severity of depression and change in depressive symptoms [24]. It is a clinician-rated scale and takes about 20–30 min to complete. The 17 items of HRDS, a score of 0–7 is generally accepted within the normal range, (or in clinical remission), whilst a score of 20 or higher (indicating at least moderate severity) is usually is required medical intervention (entry into a clinical trial). Subjects rate their responses using a Likert 4-point category scale, for example, 0 = "absent", 4 = "attempts at suicide". This is a widely used clinical assessment tool to assess the responsiveness to intervention, e.g. antidepressant drug therapy.

Brief Assessment Schedule Depression Cards (BASDEC)

BASDEC is a valid screening tool for depressive symptomatology in elderly medically ill patients [25]. It consists of a 19-item deck of cards, self-administered

as "true", "false" and "I do not know" responses. Two items are weighted to 2 points; other affirmative responses, 1 point; and "I do not know" 0.5 point with a maximum score of 21. A score of seven or above suggests a "case" of depression [25]. The BASDEC demonstrated a good response when tested against the "gold standard" of the Geriatric Depression Score (GDS) which is recommended as an assessment scale for elderly people by the British Geriatrics Society/Royal College of Physicians [26]. The BASDEC performed well as a screening tool in elderly medically ill inpatients compared with the GDS having a sensitivity of 71%, a specificity of 88%, a positive predictive value of 74% and a negative predictive value of 86% [25]. Studies suggest that BASDEC is user-friendly and can be administered by a non-medical personnel. It takes about 4 min to complete. The BASDEC scale has been validated in patients with COPD. The BASDEC scale performed well against the GMS: having a sensitivity of 100%, a specificity of 93%; a positive predictive value of 91% and a negative predictive value of 100% [23]. The kappa score of BASDEC $\geq$7 against GMS $\geq$3 was 0.93. However, the BASDEC has not been adequately tested to test the efficacy of clinical intervention in patients with COPD. The minimal clinical importance difference is unknown.

Centre Epidemiologic Scale for Depression (CES-D)

The centre epidemiologic scale for depression (CES-D) is a self-complete questionnaire comprising of 20 items. Each item has a 4-point response choice ranges from 0 to 3. A total score of $\geq$16, out of 60 points, is considered to indicate the presence of depression [27]. In addition, the CES-D score can be employed as a continuous measure where higher scores are indicative of elevated depressive symptoms. It measures the presence of depression into three categories: normal, i.e. not depressed (0–15); mild (16–21); and moderate-to-severe depression (>21) [27]. In a recent study, it was found that CES-D has a sensitivity of 80% to identify major depression and a specificity around 70% [28] in COPD patients. However, further work is required to examine the efficacy of CES-D to detect clinically relevant change following an intervention in patients with COPD.

Beck Depression Inventory (BDI)

Beck's depression inventory (BDI) is a 21-item self-administered rating inventory measuring attitudes and symptoms of depression, with high internal consistency, and good discriminates and convergent validity [29, 30]. It is scored 0–3, with the scores range from 0 to 63. The optimal cut-off score in the BDI $\geq$19 distinguishes patients with minimal or mild depressive symptoms from patients with moderate or severe depressive symptoms [30]. This cut-off point was previously used in a recent prospective study that enrolled COPD patients in a randomised controlled clinical

trial [30]. It has been recommended as a clinical screening tool for depression in COPD patients by the American College of Chest Physician [31].

Anxiety

Anxiety may be defined as an apprehensive anticipation of danger or stressful situations associated with excessive feelings of dysphoria or somatic symptoms of tension. Symptoms of anxiety include feelings of restlessness, difficulty concentrating, muscle tension, fatigue, irritability and sleep disturbance. Panic is characterised by a sudden onset of physical symptoms including breathlessness, chest pains and trembling sensations, alongside psychological symptoms that include intense fear, fear of dying and detachment [13].

Two of the most prevalent and recognisable anxiety disorders in patients with COPD are generalised anxiety disorder (GAD) and panic disorder (PD) with or without agoraphobia, which affect up to 33 and 41% of patients, respectively [32]. In contrast, the prevalence of GAD among community-based older adults is between 1 and 7%, whilst the prevalence of PD (with or without agoraphobia) is between 0.1 and 2% [33, 34]. Estimates of anxiety prevalence based on threshold scores on self-report anxiety scales suggest that clinically significant symptoms of anxiety may be present in up to 74% of patients with COPD [23].

Despite the high prevalence of anxiety disorders in patients with COPD, there has been surprisingly little focus upon anxiety within the literature. This is also the case among the general elderly population, where anxiety remains less well studied than other psychiatric disorders such as depression [35]. Findings from a recent study by Kunik et al. [36] indicate that anxiety is less recognised than depression in patients with COPD. Kunik et al. [36] found that 43% of patients with a depressive disorder had been previously diagnosed, compared to only 29% of patients with an anxiety disorder.

There is growing evidence to suggest that co-morbid anxiety in patients with COPD impacts negatively on a number of key measurable outcomes including functional status, health-related quality of life (HRQoL) and healthcare utilisation [37–39]. Anxiety may also be a major predictive factor for increased hospital admissions for acute exacerbation of COPD (AECOPD) in the elderly [23]. Anxiety also has a significant emotional impact in patients with COPD. Qualitative accounts from patients with COPD indicate that co-morbid anxiety is associated with intense fear, inextricable breathlessness and near-death experiences [40–42]. However, remarkably little is known about how patients with COPD experience anxiety, particularly which symptoms are most common and how these interact with respiratory disease.

The “gold standard” diagnosis of anxiety is through psychiatric interview with a qualified practitioner, yet this is often impractical due to the time-consuming nature of the interview. Therefore, routine screening for anxiety is typically undertaken using specifically designed scales, which can identify patients who may have

clinically significant symptoms of anxiety requiring further investigation. Current clinical guidelines for COPD, such as those from the American College of Chest Physicians [31] and Global Initiative for chronic Obstructive Lung Disease [43], advocate routine screening for anxiety. Yet, although there are a number of anxiety screening scales in existence, co-morbid anxiety remains poorly recognised and undermanaged [31, 43, 44]. For example, Kunik et al. [36] found that among 204 patients with COPD and clinically significant anxiety or depression, only 31% were receiving treatment. Furthermore, only 46% of patients with severe anxiety or depression were receiving treatment [36]. In another chart review of 102 patients with COPD, only 47% of patients with a clinical anxiety disorder were identified and followed by primary care providers or mental health providers [44].

Diagnostic Criteria for Anxiety Syndromes

The DSM-IV criteria [12] define generalised anxiety Disorder as follows:

- Excessive anxiety and worry (apprehensive expectation), occurring more days than not and for at least 6 months, about a number of events or activities (such as work or school performance).
- The person finds it difficult to control the worry.
- The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months). Note: only one item is required in children.

(1) restlessness or feeling keyed up or on edge.
(2) being easily fatigued.
(3) difficulty concentrating or mind going blank.
(4) irritability.
(5) muscle tension.
(6) sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep).

- The focus of the anxiety and worry is not confined to features of an Axis I disorder. For example, the anxiety or worry is not about having a panic attack (as in panic disorder), being embarrassed in public (as in social phobia), being contaminated (as in obsessive compulsive disorder), being away from home or close relatives (as in separation anxiety disorder), gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatisation disorder), or having serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during post-traumatic stress disorder.
- The anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or general medical condition (e.g. hyperthyroidism)

and does not occur exclusively during a mood disorder, a psychotic disorder or a pervasive developmental disorder.

Researchers and clinicians, who recognise the need to identify patients with clinically significant anxiety and/or to measure anxiety levels to monitor interventions, have called for a reliable and easily administered screening and measurement tool [36, 45]. However, as Jain and Lolak asserted [46] in 2009, the most appropriate "gold standard" anxiety screening instrument for patients with COPD was yet to be identified. The majority of anxiety screening instruments that are used in clinical practice and within research settings have been developed in and for young healthy populations. Few scales have been specifically developed for use in elderly populations and none have been developed specially for patients with COPD where there is a lack of standardisation of appropriate measures [47]. Clinical guidelines recommend scales such as the Hospital Anxiety and Depression Scale-Anxiety (HADS-A [48]), Beck Anxiety Inventory (BAI [29]) and Depression Anxiety Stress Scales (DASS [49] for measuring and screening anxiety in patients with COPD. However, these scales, although popular within COPD-related research and clinical practice, have a number of documented shortcomings that may make them unsuitable for use in patients with chronic somatic disease, particularly COPD.

Whilst all people experience anxiety to some degree, most do not develop long-term anxiety disorders. Chronic, persistent or severe anxiety is typically classified, in terms of a medical approach, into one of the specific anxiety disorders (PD or GAD, for example), such as those proposed by the DSM-IV-TR criteria [12] or International Classification of Diseases-10 world health organisation [50]. This categorical system allows clinicians to decide whether or not to treat the patient. However, McDowell [51] posits that psychologists, in contrast to medical doctors, typically take a dimensional approach to anxiety, which treats the associated symptoms of anxiety on a continuum of severity. This distinction is characterised by the two styles of measurement: the medical model of dichotomous case or non-case, categorised by a clinical diagnosis, and the psychological model of ordinal measurement of symptom severity, often measured using scales and questionnaires.

Steps for Anxiety and Depression Management

GOLD [43] and NICE [52] guidelines recommend that all newly diagnosed COPD patients should undergo a detailed medical assessment, including the assessment of anxiety symptoms. The NICE [52] guidelines for COPD also indicate that clinicians should be alert to the presence of anxiety or depression in their patients. However,

these COPD-specific guidelines fail to recommend clear strategies for identifying anxiety in this patient group. Although NICE (2010) guidelines [52] on the management of GAD and PD (with and without agoraphobia) recommend that a formal diagnosis of anxiety should be undertaken using a structured clinical interview, this is not always practical. Therefore, it is recommended that COPD patients seen in clinical settings are screened using self-report screening tools [31]. In clinical settings, a two-step approach is often incorporated in which patients are first screened using brief, inexpensive scales. Those patients who screen positive for anxiety usually undergo a more thorough assessment to confirm diagnosis with a clinical interview [53].

There are a number of barriers to the detection of anxiety and depression in patients with COPD. These typically fall into patient- or clinician-level barriers. Patient-level barriers to anxiety and depression detection include the stigma associated with mental illness which may lead patients with anxiety to exaggerate somatic complaints instead of acknowledging emotional problems, the reluctance to disclose anxiety symptoms and the confusion or masking that may occur in physical symptoms. Clinician-level barriers include the lack of a standardised assessment approach for patients with COPD, the lack of a disease-specific screening tool, the poor utilisation and uptake of existing screening tools, lack of confidence, skills and knowledge of anxiety symptoms and disorders, and the stigma of mental illness [1, 31, 36].

Such barriers may help to explain why in one recent study exploring the prevalence of anxiety disorders in patients with COPD, less than a third (29%) of patients with a clinical anxiety disorder had received a physician's diagnosis [36].

In clinical practice and research settings, monitoring of anxiety symptoms and screening of anxiety disorders is typically undertaken using self-report anxiety scales. The following section focuses specifically on these scales and critically discusses their use in patients with COPD.

Extant Anxiety Scales

There are number of different scales have been utilised for the measurement and screening of anxiety symptoms and disorders in patients with COPD. Within this section, we critically review five scales that have been either recommended by clinical guidelines for COPD, are widely utilised in COPD-related research and/or are validated for use in patients with COPD (see Table 3.2). A summary of the scales' psychometric properties is provided, with a focus on reliability and validity. Also, where appropriate, recommended cut-off values will be discussed in order to assess the clinical utility of these scales to screen for anxiety disorders.

Beck Anxiety Inventory (BAI)

Beck et al. [29] inventory is a self-report measure that was specifically designed to minimise confounding symptoms with depression and avoid the non-specific dimension of negative affect. The scale contains 21 items, with 14 items reflecting somatic symptoms of anxiety and panic. The BAI is recommended by the ACCP as a viable screening tool for use in COPD patients [31]. A few studies have utilised the BAI in COPD-related research [37, 54], yet the scale remains one of the most common instruments for measuring anxiety in general medical research [55].

Items are presented as a list of symptoms with respondents asked to rate on a four-point scale how much they have been bothered by each symptom in the preceding week. Scores range from 0 to 63. Beck and Steer's [56] manual suggests that a cut-off point of ≤ 9 indicates normal levels of anxiety; 10–18 mild-moderate levels of anxiety; 19–29 moderate-severe levels of anxiety, and 30–63 severe levels of anxiety.

The reliability of the BAI appears to be very high. A review by McDowell [51] found 16 studies reporting Cronbach's α for internal consistency of 0.86–0.94 across a range of populations, including elderly medical outpatients, psychiatric patients and healthy populations. Test-retest reliability for the BAI is reported to be 0.73 for one week and 0.67 for 11 days [57].

The factor structure of the BAI has been explored by Hewitt and Norton [58] and Creamer et al. [59] with both studies finding a two-factor solution: one factor of cognitive symptoms and a second factor representing somatic symptoms. McDowell [51] reviewed studies reporting on the convergent validity of the BAI and found correlation coefficients of 0.44–0.68 with the STAI and 0.47–0.67 with the Hamilton Anxiety Rating Scale for Anxiety. Steer et al. [60] explored whether the BAI could distinguish between elderly medical patients (without psychiatric disease) and psychiatric outpatients to establish whether the high number of somatic symptoms in the BAI may lead to false positives. Although the BAI performed generally well in discriminating between groups, the authors note that six of the somatic items did not distinguish between medical patients and psychiatric patients.

Although Beck et al. [29] claim that the BAI can be used both as a screening tool for anxiety disorders and as an outcome measure for anxiety symptoms, others contend that the BAI is not a measure of anxiety in general but rather a measure of symptoms of panic [61]. The BAI appears to have good face validity for symptoms of PAs, querying 10 of the 14 symptoms listed in DSM-IV-TR classification [12]. However, it has limited face validity for detecting GAD, as it does not include worry-type symptoms that are integral to a DSM-IV-TR diagnosis [62]. This assertion is supported by a recent FA, which suggests that the strongest quality of the BAI is to assess panic symptomatology [63]. Leyfer et al. [63] conclude that whilst the BAI has achieved significant discriminant validity for detecting patients

with PD, it has sacrificed construct validity for assessing overall anxiety. This is probably because Beck et al. [29] deliberately excluded items which may overlap with depression, particularly symptoms associated with GAD (e.g. restlessness, irritability or fatigue). Cox et al. [61] argue that the BAI is compromised as a tool for measuring general anxiety and should be considered a measure of panic.

Geriatric Anxiety Inventory (GAI)

The GAI [35] is a recently developed scale which was designed specifically for use in older populations. It was designed to minimise fatigue by being brief, minimise symptom overlap of medical conditions by excluding somatic items, and utilises a dichotomous scoring format for ease of use in patients with mild cognitive impairment. The GAI is a 20-item scale consisting of statements with an agree/disagree response format. Respondents are asked to reflect on the previous week when answering the items.

Although the GAI has only recently been developed, there are some early data relating to the scale's reliability and validity. Pachana et al. (2007) report [35] a Cronbach's α for internal consistency to be 0.91 and 1-week test-retest reliability of 0.91 in a geriatric psychiatric sample. Other studies exploring the psychometric properties of the GAI in patients with Parkinson's disease have found a Kuder–Richardson coefficient of 0.95 [64], whilst Cheung et al. (2012) report [65] a Cronbach's α of 0.92 in patients with COPD.

Pachana et al. [35] demonstrated that the GAI correlated significantly with a number of extant scales including the BAI and STAI. The optimal cut-off score for identifying patients with an anxiety disorder was found to be 8/9, which correctly classified 78% of patients with a sensitivity of 73% and a specificity of 80%. However, a study exploring the sensitivity and specificity of the GAI in detecting anxiety disorders in older patients with COPD has recently been undertaken that found a significantly lower cut-off score of 2/3. This correctly identified 80% of the sample with a sensitivity of 86% and a specificity of 78% [65].

Although Pachana et al. [35] claim the original GAI is unidimensional in nature, they present no empirical data to support this assertion. In response, a study exploring the psychometric properties of the Spanish version of the GAI found three factors: cognitive symptoms, arousal-related symptoms, and, perhaps surprisingly considering the conceptual model of the scale, a factor containing somatic symptoms [66]. Four of the items of the GAI loaded predominantly onto the somatic factor indicating that the GAI may indeed have a confounding somatic element. Item 7 "I often feel like I have butterflies in my stomach", item 12 "I get an upset stomach due to my worrying" and item 18 "I sometimes feel a great knot in my stomach" all had factor loadings of >0.7 which suggests that these stomach-related items do not fit the non-somatic model of anxiety originally proposed by Pachana et al. [35].

Hospital Anxiety and Depression Scale (HADS)

The HADS [48] was designed as a self-assessment scale for detecting clinically significant anxiety and depression in outpatients. It is widely used in general medical settings and is the most frequently utilised scale in the COPD literature. A recent review exploring the prevalence of anxiety symptoms in patients with COPD found nine studies that utilised the as a screening tool for depression and anxiety [1]. The HADS has also been recommended by the ACCP [31] and GOLD (2013) for screening [43] anxiety and depression in COPD populations.

The HADS contains 14 items covering both anxiety and depression, with patients asked to recall their experiences during the past week. The anxiety component of the HADS (the HADS-A) contains seven items: three items referring to fear or panic and four items referring to generalised anxiety. Scores range from 0 to 21 for the anxiety subscale. The depression component of the HADS (the HADS-D) comprises of seven items for depressive symptoms, with scores range from 0 to 21. A major innovation in the development of the HADS was the deliberate exclusion of symptoms that might arise from the somatic aspects of illness. This ensured that the scale (in theory) is not be confounded by physical symptoms of illness or disease [67].

Zigmond and Snaith [48] originally proposed a cut-off score of ≥ 8 as a possible case of anxiety, and ≥ 11 for a definitive case. More recently, Bjelland et al. [68] and Bunevicious et al. [69] report that a score of ≥ 9 represents the optimal cut-off point for clinically significant symptoms of anxiety. However, Bunevicious et al. [69] also found that the optimal cut-off points varied depending on the type of anxiety disorder being screened. For example, the optimal cut-off point for patients with PD was ≥ 11 yet the score was ≥ 9 for phobias and GAD. Other studies have demonstrated that optimal cut-off points in older patients with COPD may be considerably lower, perhaps as low as ≥ 4 [65].

The internal consistency of the HADS is generally moderate-high with reported Cronbach's α for the anxiety subscale of 0.76–0.93 in patients with chronic disease [68]. Quintana et al. [70] demonstrated a Cronbach's α of 0.86 for both the anxiety and depression subscales. Test-retest reliability has been reported as 0.84 at two weeks, 0.73 at two to six weeks and 0.70 at >6 weeks [71].

The validity of the HADS has been extensively tested. In terms of factorial validity, the majority of studies have found a two-factor structure for the scale, corresponding to "anxiety" and "depression" [68, 70]. However, other studies have found a three-factor solution indicative of the tripartite model of anxiety and depression [72, 73].

Although there is consistent support of the HADS for the purposes of clinical screening of anxiety disorders and measurement of the severity of anxiety symptoms, there is growing concern regarding the scale's validity and reliability in populations with illness and disease [67]. In particular, Martin highlights that if the bi-dimensionality of the HADS is not supported, or found to be compromised in certain clinical populations, then the scale cannot be concluded to reliably and accurately measure the two domains of anxiety and depression. A review of the

HADS by Bjelland et al. [68] supported the use of the HADS in a range of settings (including primary care, acute care and psychiatric populations), yet only 11 of the 20 studies they review support a bi-dimensional factor structure. A more recent review that focussed on studies from the year 2000 onwards found that only seven of 22 studies report a bi-dimensional structure [67]. The majority of contemporary studies report a 3-factor structure, yet one study by Karimova and Martin [74] found that in a sample of pregnant women ($n = 100$) there were 4–5 factors underlying the HADS. In addition, even among those studies who report a bi-dimensional structure, there were a number of instances where items loaded onto the "wrong" factor [67].

State-Trait Anxiety Inventory (STAI)

The STAI [75] is a 40-item scale measuring transient and enduring levels of anxiety. The first 20 items measure situational or state anxiety with respondents asked to indicate "How you feel right now, that is, at this moment". The second 20 items refer to underlying or trait anxiety for which respondents are asked to indicate "How you generally feel". The time frame for the state questions is "right now", which may yield problems when assessing patients with PD outside the context of a PA [62]. Each item on the STAI is scored on a four-point scale and totals for the trait and state subscale range from 20 to 80.

The STAI is used frequently within the COPD research, both as an outcome measure [76] and as a screening tool [77]. It is also the most commonly used anxiety measure in contemporary medical research [55]. Reliability for the scale is generally good. McDowell [51] reviewed a number of studies exploring the internal consistency of the STAI, the majority of which were in healthy student populations, and found Cronbach's α of between 0.83 and 0.95 for the state scale and 0.67 and 0.95 for the trait scale. Predictably, test-retest scores for the state scale are lower than those for the trait scale. For example, McDowell [51] reports 30-day retest values ranging between 0.71 and 0.75 for the trait scale and 0.34–0.62 for the state scale.

To assess the validity of the scale, Vagg et al. [78] conducted a factor analytic study of the STAI and found a four-factor structure that distinguished between state and trait anxiety and between positively and negatively worded items. However, a Rasch analysis in the mid-1980s showed that a number of items on both the state and the trait scales did not meet the scaling criteria and that there was inadequate coverage at the low end of the anxiety continuum [79]. More recently, it has been suggested that the STAI is not specific to anxiety. Rather, McDowell [51] suggests that the STAI correlates more highly with depression scales than with anxiety scales such as the BAI.

Results from a FA conducted by Bieling et al. [80] suggest that the trait part of the STAI does not assess "pure" anxiety, but rather includes items that reflect depression and general negative affect. The authors found a hierarchical factor structure with a principal factor representing negative affect and two secondary factors reflecting anxiety (items representing rumination, worry and disturbing thoughts) and depression (items representing dysphoric mood and negative

self-appraisal). A more recent FA found poor fit for the two-factor model and instead proposed a five-factor model: a 10-item anxiety factor containing three related subfactors (restlessness, self-confidence and worry), a four-item unsuccessfulness factor and a six-item happiness factor [81].

Kvaal et al. [82] assessed the state subscale of the STAI in screening for anxiety disorders among stable geriatric patients. Their results suggest that the optimal cut-off score is 54/55, with a sensitivity of 0.82 and a specificity of 0.88. The STAI contains a high number of items for a self-report measure. However, Leentjens et al. [62] argue that some of the symptoms of anxiety disorders such as GAD, PD and phobias, such as fatigue, concentration and irritability, are not represented in the state scale, limiting the face and content validity of the STAI as a generic measure of anxiety.

Anxiety Inventory Respiratory Disease (AIR)

The AIR comprises 10 items, self-administered covering anxiety symptoms, with patients asked to recall their experiences during the past two weeks [83]. It is developed with a Likert type of response 0–3. Scores range from 0 to 30. The AIR is a disease-specific tool to assess anxiety in COPD patients with deliberate exclusion of symptoms that might arise from the somatic aspects of illness. It takes about 3 min to complete the scale.

The AIR has high internal consistency (Cronbach's $\alpha = 0.92$) and test-retest reliability (ICC = 0.81), and excellent convergent validity, correlating with the Hospital Anxiety and Depression Scale-Anxiety subscale ($r = 0.91$, $p < 0.001$). A cut-off score of 14.5 yielded a sensitivity of 0.93 and specificity of 0.98 for detection of clinical anxiety [84]. This is a promising screening tool to assess anxiety in patients with COPD. It is a reliable and valid scale for measuring and screening anxiety in patients with COPD. A recent study [85] examined the responsiveness of the AIR scale to eight weeks outpatient pulmonary rehabiliation (PR) program. The AIR scale was sensitive to change following PR. Change in AIR was significantly correlated to change in quality of life (using the St. Georges Respiratory Questionnaire) and dyspnoea. The effect size of AIR was 1.01 and minimal clinical important difference was 5.55.

General Limitations of the Scales

Although some extant scales have been designed specifically to omit somatic anxiety symptoms, it is evident that none have so far achieved this goal. Both the HADS and the GAI were based on a cognitive model of panic, yet results from CFAs reveal that each scale contains items that load onto somatic factors. Scales such as the BAI and STAI include somatic items in varying proportions. The BAI is heavily weighted towards measuring somatic symptoms and contains 14 somatic items out of a total of 21.

The fact that extant anxiety and depression scales measure somatic symptoms is not a problem in the majority of settings. On the contrary, somatic symptoms are key considerations for the diagnosis of a range of anxiety and depression disorders. For example, GAD is characterised by fatigue and muscle tension, whilst PD is characterised by PAs that are dominated by somatic symptoms including palpitations, breathlessness and sweating [12]. However, these anxiety symptoms mirror the common symptoms experienced by patients with COPD and may confound the diagnosis of anxiety. According to Hill et al. [86], anxiety and depression scales [86] that contain somatic items such as breathlessness and fatigue are likely to overestimate the prevalence of anxiety and depression (i.e. create false positives), since some symptoms may be associated with the primary respiratory component. Coffman (2002) adds [87] that further confusion can be caused by the side effects of medications. For example, bronchodilators used by patients with COPD can cause tremor, palpitations and insomnia, which can be associated with symptoms of anxiety. Without a formal psychiatric interview, it is difficult to establish to the cause of somatic symptoms, and therefore, scales containing somatic items may have a limited clinical utility in this population.

In an effort to distinguish between anxiety and depression, the BAI focus upon symptoms which are specific to anxiety. In addition, the BAI focuses upon psychophysiological symptoms of anxiety which can help to distinguish between anxiety and depression. The scale focuses upon symptoms of hyperarousal such as inability to relax, heart palpitations and tremor. Subsequently, those patients with high levels of cognitive anxiety may be underrated, whilst those exhibiting high levels of somatic symptoms may be overrated [51].

The strong correlations between BAI and depression scale means that it is likely that there is a common underlying negative factor. Therefore, it is impossible to separate anxiety and depression completely [51]. It is possible, however, that efforts to discriminate between anxiety and depression have resulted in scales that do not cover the full range of anxiety symptoms. For example, Cox et al. [61] argue that the somatic-dominated BAI represents somatically laden panic rather than more general (cognitive) symptoms of anxiety. It is posited that both the DASS and the BAI measure symptoms of the majority of anxiety disorders with the exception of GAD [51].

Scales such as the HADS appear to cover a more general range of symptoms, including items relating to fatigue and irritability, but this can lead to cross-loading between anxiety and depression factors. Factor analysis of the HADS demonstrates that there is a general negative affect factor underlying the scale and this, in theory, may limit the specificity of the HADS for detecting and discriminating between anxiety disorders and depression.

Validation in Patients with COPD

Perhaps the most important limitation to the clinical utility of existing anxiety and depression scales is that few have been validated in patients with COPD. This is an

especially important consideration as scales may perform very differently between clinical populations and identical item/scale performance cannot be assumed between groups [88]. For example, the majority of extant anxiety scales were developed for general use, e.g. HADS for use in medical outpatients.

Of the six scales that have been recommended for use, or are frequently used in patients with COPD, only the BAI, GAI and the HADS have been validated (in a limited fashion) in this patient group [36, 65]. However, no studies have specifically sought to explore the reliability or validity of these anxiety scales in patients with COPD. Cheung et al. (2012) and Kunik et al. (2005) have explored [36, 65] the ability of the GAI, HADS and BAI to screen for the anxiety disorders in patients with COPD. The AIR is a new scale that has been developed for screening anxiety for patients with COPD. It is quite a promising tool. However, its clinical utility and responsiveness to intervention has not been tested for patients with COPD.

Although the HADS is recommended by NICE and AACP guidelines and is likely to be the most commonly used scale among clinicians and researchers working with patients with COPD, Cheung et al. (2012) suggest [65] that there is sufficient doubt in its ability to screen anxiety disorders accurately in older populations (particularly those with COPD) for it not to be recommended for clinical or research purposes.

Summary

It is clear that although all of the scales reviewed have promising reliability and validity in general medical populations, or in the populations they were designed for, few, with the exception of the AIR, BASDEC, BAI, GAI and HADS have been partially validated in patients with COPD. The ability of these three scales to screen for clinical anxiety and depression in patients with COPD demonstrates that none has particularly high sensitivity. In addition to the lack of validation in patients with COPD, all of the scales reviewed have limitations in one or more key areas, including the inclusion of somatic items, selective symptom coverage and questionable factorial validity. The AIR scale was responsive following PR in short term. However, its efficay in long-term follow-up is unknown. Therefore, further work is needed to validate a disease-specific anxiety and depression scales for patients with COPD.

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Chapter 4
Anxiety and Depression in COPD Patients

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Introduction

COPD exacts a devastating emotional toll from its victims. Coupled with the physical disability imposed by airflow limitation, the psychological disturbance cripples COPD patients.

Minor psychological symptoms are present in almost all COPD sufferers; specific psychiatric disorders are also quite common. This chapter focuses on depression and anxiety disorder in COPD.

Epidemiology

A complex, circular relationship exists between COPD and psychiatric disorders. Patients with mental illness are more likely to develop COPD in that they are twice as likely to smoke as the normal adult population; smoking, as is well known, is the major risk factor for COPD [1, 2]. Depressed patients appear to have a propensity for smoking, and nicotine addiction seems to worsen depression [3]. Poor

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respiratory function and chronic respiratory diseases, including COPD and asthma, are associated with increased prevalence of somatic complains, panic disorder, depression, and risk of suicidality [3, 4]. Impairment of cognitive executive function, along with quality of life, appears to be common in COPD; as many as 50% of these patients suffer from mental disease [5–10].

Estimates of the prevalence of specific mental disorders vary considerably in COPD. Differences in methodology—including sample size variation, disparity in diagnostic and assessment tools for psychiatric disorders used in different studies, and the dissimilar rates of non-participation across studies—and the difficulty in differentiating psychological symptoms from those due to COPD itself (e.g., dyspnea, fatigue, sleep disturbances) contribute to this variation in prevalence estimation.

Anxiety Disorders

Feelings of apprehension and anxiety are quite common in COPD [11–14]. Specific anxiety disorders occur in a significant proportion of patients: generalized anxiety disorder occurs in 10–33% of COPD patients, whereas panic disorder and panic attacks occur in 8–67% [11, 14].

Depression

Feelings of helplessness, hopelessness, and frustration are common in COPD [15, 16]. Depression is possibly the most common psychiatric disorder in patients suffering from COPD [17]. A prevalence rate ranging from 6 to 42% has been found in the COPD population [18–21]. Rates of depression (and anxiety) appear to be quite high among patients with repeated hospitalizations due to acute exacerbation of COPD [22].

Pathophysiology

Anxiety Disorders

Both psychological and biological models have been proposed to explain the relationship between COPD and anxiety (Fig. 4.1).

The carbon dioxide sensitivity model postulates that central chemoreceptor hypersensitivity to CO_2, in the respiratory center of the brainstem, trigger anxiety symptoms, and panic attacks (“false suffocation alarm”) [23]. This is an attractive

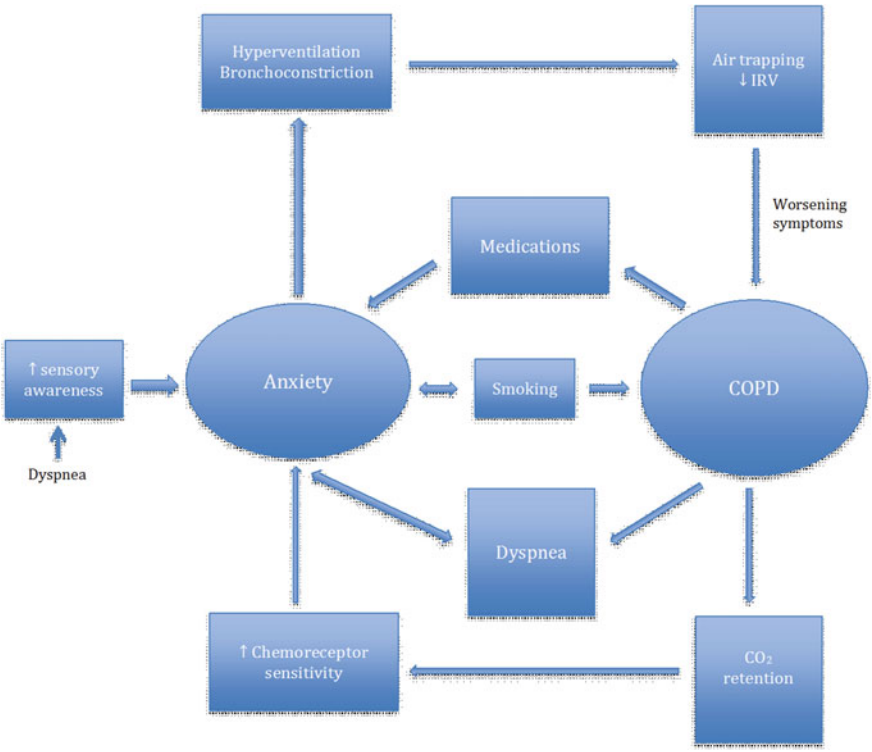

Fig. 4.1 Possible mechanisms for anxiety in COPD. *IRV* inspiratory reserve volume. Medications for COPD implicated in anxiety include steroids and beta agonists

hypothesis for panic attacks esp. in the subset of COPD patients (previously known as "blue bloaters") who are predisposed to CO_2 retention.

The hyperventilation model hypothesizes that an abnormal breathing pattern in COPD leads to dyspnea and anxiety [24]. The ensuing hypocapnia (from hyperventilation) accentuates feelings of both anxiety and breathlessness, resulting in a vicious cycle. The dyspnea-anxiety-dyspnea model proposes a similar mechanism where dyspnea—one of the cardinal features of COPD—and anxiety feed into each other [25].

The cognitive behavioral model is based on a similar premise: COPD patients misperceive their physical symptoms particularly that of breathlessness, leading to heightened awareness of arousal and exacerbation of anxiety and panic [24].

Lastly, the biological model suggests that anxiety itself causes hyperventilation and bronchoconstriction thereby worsening COPD symptoms [26].

Dyspnea appears to be the major mechanistic link between COPD and anxiety disorders. However, the severity of dyspnea does not always correlate with the severity of anxiety symptoms [27]; neither does effective treatment of dyspnea—through pharmacological or rehabilitative means—always lead to amelioration of

anxiety. This suggests that other factors also play a role in pathogenesis. One such factor could be the medications used for COPD treatment themselves, as anxiety and panic attacks could be related to beta agonist and high dose steroid therapy used in selected patients [28].

Depression

Various psychological and biological theories have been suggested for increased rates of depression in COPD (Fig. 4.2).

Firstly, COPD leads to immense fatigue and impaired mobility. These precipitate a deterioration in functional independence, as well as social and occupational decline [17]. Such handicap can cause or exaggerate feelings of depression.

Secondly, increased hypoxia in the middle-aged COPD patient population (both from the disease and smoking) leads to increased rates of depression at an older age. Persistent hypoxia in the brain can cause white matter and endothelial changes, and oxidative stress. This can result in mood changes and a decline in executive functioning, depending on the affected area of the brain [4].

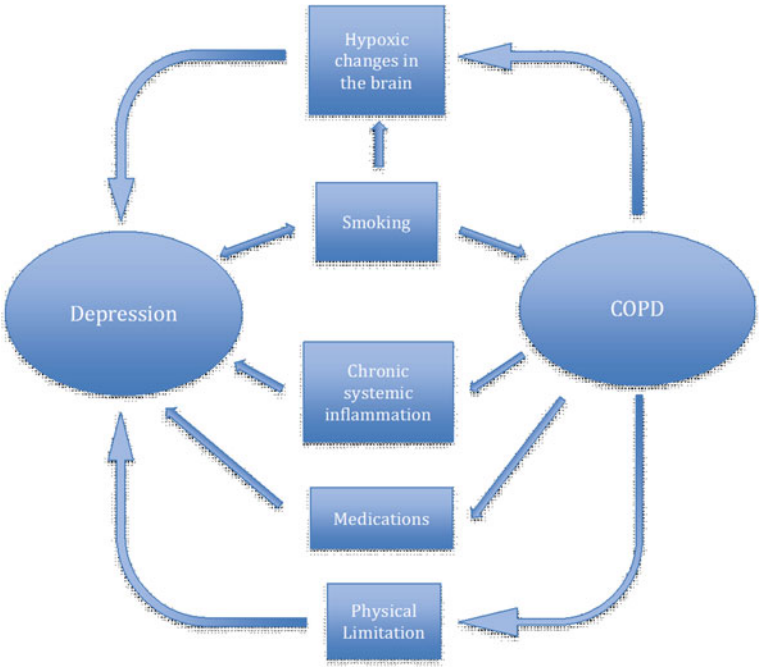

Fig. 4.2 Possible mechanisms for depression in COPD

Thirdly, a chronic systemic inflammatory state associated with COPD (with elevated C-reactive protein and cytokine levels) has also been proposed as a cause for increased rates of depression [4].

Lastly, the medications used to treat COPD can themselves precipitate or worsen mood disorders. In one study, patients with severe COPD who were receiving steroids had higher rates of depression when compared to those not on the medication [29].

Clinical Features and Implications of Psychological Disorders in COPD

There is a considerable overlap between symptoms due to COPD and those from anxiety and depression; a careful evaluation is hence necessary prior to diagnosing a psychiatric disorder in this population. Comorbid anxiety and depression adversely affect COPD patients. Longer hospital stays and impaired ambulation, mobility, sleep, and rest have been observed in COPD patients with psychiatric disorders than those without [30, 31].

Anxiety

Feelings of difficult to control anxiety and apprehension, coupled with psychosomatic complains (increased muscle tension, restlessness, sleep difficulties, fatigue, difficulty in concentration, and irritability) occur with generalized anxiety disorder. Recurrent panic attacks (acute onset, short-lived episodes with characteristic symptoms and signs of autonomic arousal and feelings of doom) are a feature of panic disorder.

Anxiety symptoms significantly impact the quality of life in COPD patients. Higher rates of hospitalization, longer length of inpatient stay, impaired physical and social functioning (with increased social isolation), and quality of life are linked with the disorder in this population [6, 32, 33]. One study suggests that, at least in females with COPD, poor emotional function may be a predictor of overall poor survival [34].

Depression

Low moods or loss of interest in previously pleasurable activities are the hallmark of depression. Other symptoms include disturbances in sleep and appetite, feelings

of guilt or hopelessness, psychomotor retardation or agitation, fatigue, impaired concentration, and suicidal ideation.

Depression is a better predictor of functional capacity as compared to physiological parameters in patients with COPD [17]. It leads to an increased frequency and length of stay in hospitalized COPD patients and increases utilization of outpatient and emergency care [35]. Ultimate medical costs for such patients rise by 50% [36]. Other than impacting the financial cost for COPD sufferers, it also detrimentally affects their quality of life, due to further impairment in social and occupational functioning.

Depression also acts as a barrier to seeking help and thus leads to worsening of the primary symptoms of COPD due to inadequate treatment. This in turn results in an exaggeration of the mood symptoms, hence, initiating a vicious cycle of deterioration.

Screening and Diagnosis

Accurate diagnosis of psychiatric illnesses starts with having a high index of suspicion for the ailments. Clinicians and healthcare workers involved in managing COPD patients should be cognizant of the high frequency of psychological disease in COPD. Patients should be referred to qualified mental health professionals when there is concern for mental illness. Screening tools serve as a useful aid in identifying such individuals. Diagnosis is made using DSM-V criteria.

Anxiety Disorders

Screening: Anxiety specific as well as global psychological assessment tools with anxiety domains are available for screening for anxiety disorders. Anxiety-specific questionnaires include the Beck Anxiety Inventory, State-Trait Anxiety Inventory, and Hamilton Anxiety Rating Scale [37, 38]. Global psychological assessment tools include the Hospital Anxiety and Depression Scale, Hopkins Symptom Check List, and Patient Health Questionnaire [39, 40].

A simple 5 question-based tool, Primary Care Evaluation of Mental Disorders (PRIME-MD), appears to be quite useful in identifying patients at risk for psychological disorders (Table 4.1) [41]. Scores above specified cut off points on these tools indicate need for further evaluation of patients; they should be referred to qualified mental health specialists.

Diagnosis: Specific diagnosis of anxiety disorders should be made by a psychiatrist, using DSM criteria (Tables 4.2 and 4.3). As mentioned earlier, there is a considerable overlap between symptoms of anxiety and those of COPD. A detailed, structured interview by a mental health professional helps differentiate symptoms due to anxiety disorders from those of the underlying COPD.

Table 4.1 PRIME-MD screening questionnaire for depression and anxiety[a]

Depression screen (PHQ-2)	In the past month, have you been bothered a lot by: 1. Little interest or pleasure in doing things? 2. Feeling down, depressed or hopeless?
Anxiety screen (PHQ-3)	In the past month, have you been bothered a lot by: 1. "Nerves," or feeling anxious or on edge? 2. Worrying about a lot of different things? During the last month: 3. Have you had an anxiety attack (suddenly feeling fear or panic)?

[a]*PHQ-2* two-item Patient Health Questionnaire; *PHQ-3* three item Patient Health Questionnaire

Table 4.2 Generalized anxiety disorder

Generalized anxiety disorder
– Anxiety and apprehension about different personal, social or occupational circumstances – Feelings of worry are out of proportion to expected norms – Symptoms are present for the majority of a minimum six month period – Symptoms include at least three of: excessive muscle tension or strain, easy fatigability, sleep disturbances/insomnia, difficulty with maintaining concentration, feelings of unease or restlessness, and irritability – Symptoms significantly affect the ability to perform well (at work, in a social setting, etc.) or result in suffering – Symptoms are not otherwise explained or caused by a medical condition, medication or drug of abuse, or by a mental condition other than generalized anxiety disorder
For specific diagnostic criteria, please refer to: American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition. Arlington VA, American Psychiatric Association, 2013, or The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines, World Health Organization, 1992

Depression

Screening: Screening tools can help identify COPD patients at risk for major depressive disorder. Several questionnaires are available, including the Beck Depression Inventrory, Zung Depression Scale, the Patient Health Questionnaire-9 (PHQ-9), the Center for Epidemiologic Studies-Depression (CES-D) scale, Geriatric Depression Scale, and Brief Depression Scale, all with reasonable sensitivity and specificity [42–47]. As mentioned above, a simple, 5 question instrument, PRIME-MD, is a good screening tool for depression and anxiety in this population [41].

Screening tools can aid physicians in identifying vulnerable patients. These patients should then be referred to a psychiatrist.

Table 4.3 Panic disorder

• Characteristic, repeated, panic attacks – Sudden feeling of intense debilitating fear and anxiety, in the absence of an obvious cause or danger. Symptoms peak within a few minutes and should include at least four of the following: feeling of doom/fear of death, palpitations, dyspnea, chest pain, sweating, shaking/trembling, choking sensation, nausea or abdominal discomfort, feeling of numbness/tingling, light-headedness/dizziness, depersonalization (feeling detached from one's body) or derealization (feeling detached from reality)
• Significant anxiety about the possibility of a recurrence of a panic attack for at least a one month period after one such episode. This anxiety can lead to avoidance behavior (typically, with the goal of not triggering further panic attacks) resulting in functional impairment • Symptoms are not otherwise explained or caused by a medical condition, medication or drug of abuse, or by a mental condition other than panic disorder
For specific diagnostic criteria, please refer to: American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition. Arlington VA, American Psychiatric Association, 2013, or The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines, World Health Organization, 1992

Diagnosis: A firm diagnosis of depression in COPD is based on a clinical interview by a psychiatrist. DSM-V and the ICD 10 are common criteria used for diagnosis (Table 4.4). Neurovegetative signs such as sleep, fatigue, and appetite problems can be misleading in identifying depression in COPD as these can be related to the primary disease itself. Loss of interest and enjoyment in pleasurable activities (anhedonia), feelings of guilt and hopelessness, and suicidal ideations, along with depressed mood, can be better indicators of depression in this population [17].

Treatment

A multidisciplinary approach—involving the primary care physician and nurse, pulmonary specialist, social worker and physiotherapist (especially those involved in pulmonary rehabilitation), and mental health professionals—is best for COPD patients with psychological disorders, as it focuses on both the patient's physical and psychological well-being. Pulmonary rehabilitation is an example of such a multidisciplinary collaborative care model and has been shown to improve exercise capacity, dyspnea severity, and health-related quality of life, including emotional function, reduction in anxiety and depression symptoms, and improved cognitive function [27, 48–50].

Table 4.4 Major depressive disorder

– Low mood and/or anhedonia associated with at least three[a] (or more) of: sleep disturbances (insomnia or hypersomnia), fatigue/low energy, feelings of guilt or low self-esteem, significant change in appetite or weight (depressed or excessive), restlessness or lethargy, suicidal ideation or preoccupation with death, or decreased ability to concentrate
– Symptoms persist for at least a two week duration
– Absence of manic or hypo-manic episode
– Symptoms significantly affect the ability to perform well (at work, in a social setting, etc.) or result in suffering
– Symptoms are not otherwise explained or caused by a medical condition, medication or drug of abuse, or by a mental condition other than major depressive disorder

[a]When both low mood and anhedonia are present. A total of five symptoms is needed

For specific diagnostic criteria, please refer to: American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition. Arlington VA, American Psychiatric Association, 2013, or The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines, World Health Organization, 1992

Clinicians should optimize medical therapy for COPD (bronchodilators, inhaled corticosteroids—when indicated—roflumilast, long-term oxygen therapy, etc.) as improved lung function and functional capacity impact psychological symptoms favorably. Treatment of comorbid mental disease is essential; psychological disorders remain untreated in a significant portion of COPD patients [10, 51].

Psychiatric help is especially useful when psychological symptoms are severe and refractory, there is concern for drug interaction with complex regimen in the elderly, or with suicidal ideation.

Anxiety Disorders

Non-pharmacological Therapy

Mixed results have been observed with psychotherapy for anxiety disorders in COPD [33, 52, 53]. Cognitive behavior therapy aims to correct distorted views about life experiences in COPD patients whereby emotional distress magnifies the physical handicap and symptoms due to the chronic respiratory illness. Progressive muscle relaxation (with or without breathing exercises and disease specific education), attempts to reduce anxiety by decreasing muscle tension. Improvement in anxiety symptoms was observed in a few studies with the above measures; other studies have not demonstrated any conclusive benefit with these therapies [54–56].

Data for efficacy of pulmonary rehabilitation in reducing emotional distress appear to be more robust [27, 33, 35, 57–60].

Pharmacotherapy

It is important to differentiate between symptoms due to a true anxiety/panic disorder versus panic due to severe dyspnea secondary to exertion in patients with limited functional pulmonary reserve in stage III and stage IV COPD. Medications help for the former, whereas education about recognizing functional limitation and changes in perception (to break the dyspnea-anxiety-dyspnea cycle) may be more useful for the latter.

Very few rigorous, randomized studies have been conducted on medication use for anxiety disorders in COPD. Similar to treatment for anxiety disorders with no comorbids, psychotropic medications—selective serotonin reuptake inhibitors (SSRIs) (Table 4.5), serotonin receptor agonists (buspirone), and tricyclic antidepressants (TCAs)—are used in clinical practice as pharmacotherapy for anxiety in COPD. The serotonergic effect of these medications (well established esp. for clomipramine) potentially decreases central chemoreceptor CO_2 sensitivity and ameliorates panic attacks [23]. SSRIs appear to be well tolerated [61, 62]. Data on efficacy, however, is equivocal [63, 64]. Caution should be exercised when using TCAs, especially in the elderly, due to potential cardiac toxicity.

Rarely, benzodiazepines, in low doses, can be used for anxiety symptoms refractory to above medications. Clinicians should apply extreme caution when using benzodiazepines, esp. in hypercapnic patients, as these can cause respiratory depression [24].

Depression

Non-pharmacological Therapy

Options, similar to those available for anxiety, include pulmonary rehabilitation and psychotherapy. Pulmonary rehabilitation, as mentioned, improves quality of life and emotional function [65, 66]. Cognitive behavioral therapy also appears to hold promise for improving depression symptoms [52].

Pharmacotherapy

Currently, depression in COPD is treated with standard antidepressants that are used in the non-COPD population as well. SSRIs are commonly used and are well tolerated (Table 4.5). TCAs, particularly Imipramine and Amitriptyline, can also be used; data on their usefulness, however, is inconclusive [67, 68]. Common side

Table 4.5 Commonly used medications for depression and anxiety in COPD

	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline	Buspirone
Usual daily dose (depression)	20–40 mg	10–20 mg	10–20 mg	20 mg	50 mg	
Usual daily dose (anxiety)	N/A	10–20 mg	10–20 mg	20 mg	N/A	20–30 mg
Common Side effects	Nausea Dry mouth Somnolence Insomnia Diaphoresis Diarrhea	Headache Nausea Insomnia Diarrhea Ejaculation disorder	Nausea Headache Insomnia Nervousness Anxiety Drowsiness Dizziness Diarrhea	Nausea Somnolence Headache Dry mouth Dizziness Weakness Fatigue Sexual dysfunction Diaphoresis Diarrhea Insomnia Anorexia	Nausea Headache Insomnia Somnolence Dizziness Diarrhea Dry mouth Sexual dysfunction (ejaculation failure, decreased libido) Fatigue	Nausea Dizziness Drowsiness Headache Nervousness
Other important adverse events	Tremor Sexual dysfunction (abnormal ejaculation, decreased libido, impotence) Fatigue Anxiety Anorexia Arrhythmias EPS	Sexual dysfunction (decreased libido, impotence) Dry mouth Drowsiness Fatigue Diaphoresis Dizziness Anxiety	Weakness Dry mouth Anxiety Agitation Tremor Increased sweating	Tremor Constipation Decreased appetite Anxiety Nervousness Arrhythmias EPS	Tremor Increased sweating Agitation Anorexia Nervousness Anxiety Arrhythmias EPS Serotonin syndrome	Akathisia Elevated LFTs Arrhythmias EPS Serotonin syndrome

(continued)

Table 4.5 (continued)

	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline	Buspirone
	Serotonin syndrome	Anorexia Arrhythmias EPS Serotonin syndrome	Sexual dysfunction Anorexia Arrhythmias Serotonin syndrome	Serotonin syndrome		
Potential for drug interaction	Relatively low	Relatively low	High	Moderate to high	Relatively low	Moderate

LFTs liver function tests, *EPS* extrapyramidal side effects

effects with SSRIs include gastrointestinal problems (nausea, reflux, stomach pain), headache, akathisia, and sexual dysfunction (decreased libido, ejaculation failure). Drug interactions, hyponatremia, and deranged coagulation can be problematic in the geriatric population.

Compliance to medication is usually poor [69]. Side effects, unwillingness on the patient's part to add another medication to their regimen, the embarrassment of having a psychiatric disorder and the need to take psychiatric medications all lead to problems with treatment acceptance and adherence. A comprehensive approach to treatment is beneficial in increasing compliance. Treatment programs with an assigned case manager who provides support and psychoeducation, monitors side effects and encourages adherence, are more successful than the traditional approach [17] in improving the overall standard of care of COPD.

Last, but not least, it behooves the collaborative care models for COPD treatment to keep the primary caregivers at home in mind and extend support to them as necessary.

Conclusion

COPD is associated with significant psychological morbidity. Combined with the physical disability imposed by airflow limitation, the emotional handicap can prove crippling. Mental illness is underdiagnosed and undertreated in COPD.

Screening, diagnosis and management in a collaborative care model, involving the primary care physician and nurse, pulmonary specialist, psychiatrist, case manager, and rehabilitation staff, is currently the recommended approach in providing optimal care to these patients.

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Chapter 5
Depression and Anxiety in Adult Patients with Asthma

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Introduction

Asthma is a major cause of morbidity, disability and healthcare utilization. It is estimated to affect over 300 million people [1] worldwide and has a significant impact on individual's personal, e.g. work-related activities, social interaction and quality of life. The cost of caring for moderate to severe asthma is substantial. In 2007, in the USA alone, the total cost of annual direct medical expenditure attributable to asthma treatment is estimated at approximately $37.2 billion [2].

Asthma is a multifactorial lung disease that is related to significant development of medical comorbidity. Anxiety and depression are two commonly, untreated and undiagnosed comorbidities for patients with asthma. A recent worldwide survey of 54 countries including developed and developing nations [3] reported that persistent wheezing in the past month was associated with elevated symptoms of anxiety and depression in adult patients with asthma. It also highlights the importance of addressing the 'asthma-mental health problems' as they are inadequately diagnosed and treated as a public health agenda and clinical management priorities. The prevalence of depressive and anxiety symptoms in patients with asthma are estimated to be 27 and 35% [4, 5], respectively. A recent meta-analysis [6] of 8 studies (3546 adolescents with asthma and 24, 884 controls) reported that asthmatic patients are twice more likely at risk of developing depressive symptoms and 83% more likely to exhibit anxiety symptoms compared to healthy aged-matched controls.

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In addition, panic disorder occurs at a higher rate in patients with asthma compared with the general population [7, 8]. These comorbid disorders are associated with increased physical disability, social isolation, poor treatment adherence, greater asthma symptom severity, increased healthcare utilization and premature mortality [4–8].

There is a lack of strong evidence for the management of depression and anxiety for patients with asthma. This is partly due to that current clinical practice both in primary and secondary care does not routinely screen patients diagnosed with asthma for anxiety or depression or provide specific interventions to reduce psychological distress for this patient group. In addition, there is a lack of specific guidance from current evidence-based guidelines, e.g. the Global Initiative for Asthma [9] on management of depression and anxiety in asthma.

Dyspnoea-related anxiety and exhaustion of asthma combined with the hopelessness, helplessness and depression corrode the patients' ability to adhere to their rehabilitation and other treatment regimens. Consequently, depressed asthmatic patients often continue to smoke and have frequent medical complications, increased mortality, persistent depressive symptoms and signs, disability, decreased social interactions, increased wheezing and poor quality of life [4–8]. Anxious asthmatic patients may have also difficulties in coping with the disease during exacerbations. They are most likely to access emergency healthcare services frequently and longer-hospital stay after acute exacerbations. Furthermore, poor asthma control may exacerbate the incidence of depressive symptoms [10].

Understanding comorbid diseases such as depression and anxiety in patients with asthma may help clinicians to develop appropriate prevention and treatment strategies to improve the health outcomes. Despite high prevalence and impact of anxiety and depression in patients with asthma, management of these comorbidities is often inadequate. This chapter evaluates the prevalence, management of anxiety and depression in patients with asthma. It will also outline implications for clinical practice and research.

Impact and Mechanisms of Depression and Anxiety in Asthma

Although the exact mechanism of how depression and anxiety symptoms develop (manifest) in patients with asthma is uncertain, it is most likely to be multifactorial as listed in Table 5.1. Psychiatric comorbidities including depression and anxiety in asthmatic patients have been associated with disease severity, poor adherence to medical treatment and loss of asthma control. In a two-year longitudinal study, Katz et al. [11] investigated the incidence of depression in community-based sample [$n = 439$] of adults with asthma. Using the Center for Epidemiologic Studies Depression questionnaire (CES-D $\geq$ 23), the incidence of new onset depression was 8%. Decreased in perception of asthma control was associated with the new onset of depression (odds ratio, 7.47, 95% CI 2.15–26.01). It is worth exploring the

Table 5.1 Risk factors associated with development of anxiety and depressive symptoms in asthma

Increased physical disability
Poor quality of life
Poor adherence to treatment
Prenatal smoking exposure
Low perceived control of asthma
Caucasian (white race)
Active smokers
Prednisone dependent
Severity of wheezing
Severity of respiratory impairment
Maladaptive behaviour
Female gender
Physical inactivity
Inadequate social support
Lower socio-economic status

efficacy of asthma education in subset of asthmatic patients with poor perception. However, caution is required in interpretation of these finding as CES-D is usually considered a screening tool and not a diagnostic measure.

Lavoie et al. examined [12] the prevalence of psychiatric disorders in asthmatic patients attending an outpatient clinic [$N = 504$]. Psychiatric assessment was carried out using the Primary Care Evaluation for Mental Disorders (PRIME-MD) [13], a short questionnaire that takes about 20 min to administer. About one-third of the patients met the diagnostic criteria for one or more psychiatric disorders. Eight per cent of the patients met criteria for major depression, 12% for anxiety disorder and 11% for panic disorder. In addition, 11% of these patients had both anxiety and depressive disorders. In addition, major depression was independently associated with poor asthma control (not anxiety). This signify depression compromises individual's ability initiating and managing complex treatment regimens that require sustained effort, self-monitoring and administration. Furthermore, depression may have compromised patients' active role in the family, dependency on others for activities of daily living, lowered self-efficacy and social interaction.

In a separate study, Lavoie et al. examined [14] the influence of psychological distress and maladaptive coping styles in patients [$n = 84$] with moderate and severe patients with asthma. Patients were categorized into moderate to severe lung function impairment using the standard pulmonary function testing according to American Thoracic Society/European Respiratory guidelines [15, 16]. Their findings indicate that patients with severe asthma [$n = 42$] reported high level of psychological distress, worse cognitive dysfunction, emotional coping, future pessimism and apprehension compared to moderate asthmatics [$n = 42$]. A cross-sectional study in Spain [17] from outpatient clinic of patients with asthma ($n = 354$) reported the prevalence of anxiety was 31%, depression was 2% and anxiety plus depression was 10%. Over 77% of the asthmatic patients had poor or

partial control of their condition. In addition, patients with poor asthma control are three times more likely to exhibit the risk of developing anxiety plus depression. Elevated level of anxiety was associated with impaired quality of life in patients with asthma. In a community survey [18] of older people (n = 20,888) in Norfolk, England examined the association between psychosocial factors and asthma. Out of these, 1699 (8.1%) of the participants had physicians diagnosed asthma. Major depression, adverse childhood circumstances, difficulties in adulthood and inadequate social support were associated with the chronicity of asthma. Furthermore, Bacon et al. [19] reported that asthmatic patients from the lower socio-economic status (SES) had utilized greater emergency healthcare services and worse self-asthma control compared to patients with higher SES. All these factors signify that psychosocial factors have deleterious effect on psychological well-being and impaired quality of patients with asthma.

Vazquez et al. [20] examined the influence of 'near-fatal asthma [NFA]' experience [n = 44] in stable adult patients with asthma compared to patients 'without near-fatal asthma' [n = 44], in their coping mechanism, self-management and psychological problems. Patients with asthma who experience a near-fatal experience had higher levels of trait anxiety (a tendency to perceive situations as threatening and consequently increase) and more difficulties describing and communicating feelings compared those who did not have a NFA. There was no difference in self-management in both groups. However, because of the cross-sectional nature of the study, it could not infer whether the association of psychological problems with NFA can be regarded as risk factors or a consequence of the experience of a NFA crisis [20]. Thus, longitudinal study is worthy of consideration to elucidate this point.

Work-related asthma (the cause of the stimuli is individual's work environment) is a common cause of adult on-onset asthma. It affects 9–15% of adult patients with asthma [21]. Lavoie et al. [22] in a prospective study (n = 219) using the PRIME-MD, examined the prevalence of psychiatric disorders including mood and anxiety disorders and hypochondriasis in patients referred for the occupational asthma assessment. Thirty-four per cent of the patients with occupational asthma had psychiatric disorders. Out of these, 29% mood disorders and 24% anxiety disorders were diagnosed, respectively. Seven per cent of the patients' with occupational asthma was diagnosed with hypochondriasis. In addition, hypochondriasis is associated with increased risk of not receiving any medical diagnoses. In a large survey of (n = 1267) occupational asthmatic (OA), patients who were exposed to workplace moisture and moulds had worse quality of life compared to patients without OA [23]. Furthermore, being unemployed (due to disability, retirement, job loss or other reasons) and the greater need for asthma medication were associated with poorer quality of life.

In 2010, Goodwin et al. [24] using data from the Canadian Community Health Survey Cycle 1.2 (N = 36,984; age $\geq$ 15 years) examined the association between mental health disorders and asthma and the impact of asthma and mental disorder on functional impairment and mental healthcare service use among adults in the community. Their findings indicated that asthma was related to mental health

disorders such as post-traumatic stress disorder, mania and panic disorder. Thus, asthma patients with comorbid mental health disorders had elevated rates of functional impairment and use of mental health services compared with those either asthma patients or mental health disorders. Furthermore, data that were drawn [25] from the Third National Health and Nutrition Examination Survey, a representative sample of adults ($N = 6584$) in the USA, showed that current asthma was related with an increased likelihood risk of 77% suicidal ideation (odds ratio: 1.77, confidence interval: 1.11, 2.84) and suicide attempt (odds ratio: 3.26, confidence interval: 1.97, 5.39), respectively. Adult asthmatic patients are prone to a threefold increased risk of attempting to commit suicide compared to patients without asthma counterparts, although the exact cause(s) that instigate asthmatic patients for suicidal ideation are unknown. It is most likely multifactorial including psychosocial factors, hopelessness due to severity of asthma, elevated symptoms of depression and anxiety. Those asthmatic patients identified with suicidal ideation promptly referred to mental health services for treatment. Further studies are needed.

Management of Anxiety and Depression in Asthma

Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) has been shown to improve exercise capacity, quality of life and improve depressive and anxiety symptoms and is now considered cornerstone in the management of chronic obstructive pulmonary disease (COPD) [26]. However, the efficacy of PR in improving outcomes in patients with asthma is unclear.

A recent study [27] examined the efficacy of an 8-week home-based PR in patients with persistent asthma. Fifty-two patients (20 men and 32 women) were recruited. The intervention comprised group exercise training program, educational sessions and respiratory physiotherapy. Three quarter of the patients completed the PR programme. A statistically significant improvement in exercise capacity using the 6-min walk test (mean increase was 33 m) was observed although this change did not reach clinically significant difference, which was 54 m [28]. There were some improvement in physiological indices, e.g. in peak oxygen uptake. Twenty-five per cent of the patients did not complete the rehabilitation programme. The dropout rate was significantly higher in younger patients who were employed. There was no statistically significant improvement in health-related quality of life using the Short Form-36 (SF-36) item Health Survey. Thus, further well-controlled studies are needed to demonstrate the efficacy of PR in larger sample.

In another mixed group of asthma ($n = 7$) and COPD (13) of 3 months, outpatient PR programme three times per week, with a high aerobic intensity exercise programme and each session for two hours, was conducted [29]. There was a statistically and clinically significant improvement in exercise capacity using the 6-min

walk test and improvement in quality of life using SF-36 were observed. However, there was no improvement in anxiety and depression scores for both groups. This might be due to small sample size and unblinded nature of the study. Further studies are needed to determine the optimal frequency and intensity of PR including psychological therapy to treat the severity of depression and anxiety in patients with asthma.

Haavee and Hyland [30] examined the efficacy of 4 weeks intensive inpatient PR program to ameliorate trait anxiety (negative emotions such as fears, worries, and anxiety in different situations) and improve quality of life in patients with asthma (n = 92) and COPD (n = 40) following the program and longitudinal changes in 6 months. There was significant improvement in quality of life for both groups immediately after rehabilitation but gained improvement was diminished at 6 months. There was no change in trait anxiety scores. For both groups, significant improvement was observed in quality-of-life scores in patients who were living alone compared with those who live with spouse or partner. The findings of the study may implicate that it is important to consider maintenance exercise program following PR to achieve sustain improvement in quality of life. However, because the availability of inpatient PR is very limited in most countries in the world, and access to this type of service is unlikely to be available in the foreseeable future because of higher cost to run the programme. The cost effectiveness of the programme was not examined.

A Cochrane review [31] examined of twenty-one randomized control trials which enrolled asthmatic patients aged 8 years and over (772 participants) who participated in physical exercise training or not. Physical training had to be undertaken for at least 20 min, two times a week, over a minimum period of four week. Physical training was shown to be beneficial in improving maximum oxygen uptake. However, there were no significant improvements in lung function test or other outcome measures. More recently, another systematic review [32] examined the effects of physical training on airway inflammation in asthmatic patients. The systematic review included 23 studies (16 randomized controlled and 7 prospective cohort studies) of 2635 asthmatic patients. Generally, the study sample sizes were relatively small (with median sample size = 30). Physical training was beneficial in reducing C-reactive protein, malondialdehyde, nitric oxide, sputum cell counts and Immunoglobulin E (IgE) in asthmatics compared to patients without physical training. However, the authors have observed significant variations among the studies in terms of physical training intervention type, duration, intensity, frequency, primary outcome measures, methods of assessing outcome measures and study designs. Therefore, it was difficult to provide firm conclusion about the efficacy of physical training in asthmatic patients. Further, well-controlled trials are needed.

Cognitive Behavioural Therapy

Anxiety is a common reaction to extreme dyspnoea in patients with chronic respiratory diseases. However, uncontrolled excessive anxiety and high levels of panic may contribute to exacerbation of the condition (making it worse) and poor

management of asthma. Cognitive behavioural therapy (CBT) is an action-oriented treatment in which both cognitive (e.g. identification and challenging of interpretation errors) and behavioural (e.g. planned exposure to avoided sensations and situations) strategies are used to interrupt the panic and/or anxiety cycle and facilitate more adaptive responses [33].

Parry et al. [34] examined the efficacy CBT in 94 highly anxious adult patients with asthma that were randomly allocated to receive either a cognitive behavioural intervention to improve self-management of their anxiety symptoms ($n = 50$) or routine clinical care ($n = 44$). The primary outcome was to reduce asthma-specific fear at 6-, 12- and 24-week follow-up. Treatment was specifically designed to include education about asthma and anxiety using the CBT to improve self-management of asthma-specific fear. Their findings indicate that the CBT significantly reduced asthma-specific fear at the end of intervention and at 6 months compared to the control group. In addition, there was significant reduction in the depression score and improvement in quality of life in the CBT group at the end of intervention. However, there was no significant difference at 6-month follow-up in these parameters both in the CBT and control group. Furthermore, cost for the use of healthcare resources was not reduced (not cost-effective) in the CBT group. Thus, further studies are needed to determine the duration, frequency of CBT and the potential benefits of 'booster-sessions of CBT' in longer-treatment follow-up.

In another nurse led [35] 8 week evaluating CBT therapy in a group of 48 adult women with asthma with coexisting panic disorder was conducted with 6-month follow-up. Patients were randomly allocated to a CBT therapy ($n = 25$) or a waiting-list control group ($n = 23$). Sixty per cent of the CBT group and 44% of the control group completed the study. The CBT group showed significant improvement in their anxiety and panic scores at 8-week and at 24-week follow-up compared to the control group, respectively. However, the improvement that was achieved at 8 weeks in quality of life was not sustained at 24 weeks. This was a specific female gender study and generalizability of the findings to the wider asthma population is questionable.

Antidepressants

There is little evidence in the literature about the use of antidepressants in the treatment of depression and anxiety in patients with asthma. Only one pilot study examined the efficacy of antidepressants. In a single blind pilot study, Brown et al. [36] investigated the efficacy of bupropion 20 mg daily over 12 weeks. Eighteen depressed asthmatic patients participated in the bupropion therapy. Depression and anxiety severity were measured using the Hamilton Rating Scale for Depression (HAM-D-17) and the Hamilton Rating Scale for Anxiety (HAM-A), respectively. In total, 27.8% of the patients responded to treatment (50% reduction in the HAM-D) and 16.7% patients remitted (no depression). There was significant

correlation between changes in percentage forced expiratory volume in one second, asthma control and changes in HAM-D scores after 12 weeks of bupropion therapy. In addition, there was a statistically significant change in anxiety score (mean change = 2.12, SD = 3.97, $p = 0.04$). This pilot study demonstrated that the benefits of antidepressant to treat anxiety and depression. However, caution is required in interpretation of these findings because of small sample size and lack of a control group. Therefore, well-controlled randomized control trials are needed to evaluate the efficacy of antidepressants especially using the selective serotonin reuptake inhibitors in patients with asthma.

Implications for Research and Clinical Practice

Anxiety and depression are common comorbidities in adult patients with asthma and are associated with increased morbidity and healthcare utilization. Most of the existing data are based on studies, which are cross sectional, and there is a scarcity of longitudinal research. In asthmatic patients, anxiety and depression were associated with increased healthcare utilization, physical disability and impaired quality of life. Psychosocial assets, individual, interpersonal relationship and socio-economic status are all valuable in determining the patient's response to treatment and psychological well-being of patients with asthma. Thus, healthcare professionals should play an active role in the early diagnosis and adequate treatment of these comorbid conditions.

The exact mechanisms linking the physical burden of asthma to elevated depressive and anxiety symptoms may require further investigation in longitudinal studies.

Very few studies have investigated the efficacy of PR in the treatment of anxiety and depression in adult patients with asthma. Because of the fact that findings of these studies were mostly inconclusive, well-controlled studies are needed to examine the benefits of PR in long-term follow-up. In addition, a few studies [34, 35] have examined the role of CBT in reducing depressive, anxiety and panic symptoms in patients with asthma. CBT may have a role in treating these symptoms, but the available data and access to CBT services are scant but well-controlled studies are needed to evaluate this further. The efficacy of antidepressants for treating depression and anxiety in adult patients with asthma has not been evaluated, and thus caution is required for the judicious use of antidepressants especially patients with mild-to-moderate depression in patients with asthma. Further studies are required to determine which class of antidepressants, duration and dosage are effective in the treatment of comorbid depression and anxiety in patients with asthma.

A comprehensive treatment strategy such as collaborative care model (CCM) [case management] with partnership with patients and family has been shown to be effective in the treatment of depression in patients with chronic diseases [37]. Education about depression treatment and ongoing support from healthcare professionals is important in depressed patients with asthma and/or COPD given their reluctance to accept antidepressant drug therapy [38]. Therefore,

it is worthy to examine the benefits of CCM in patients with asthma who suffer from clinical depression and/or anxiety disorders.

Clinical Tips

1. Adult asthmatic patients with recent changes in their lifestyle (e.g. loss of loved ones, divorce) with recurrent episodes of chest infections and hospital admission should be assessed for anxiety and depressive symptoms, e.g. using the Hospital and Anxiety Depression scale [37]. Those identified with the elevated symptoms of depression HAD > 11 or anxiety HAD > 11, where by mental health services are available, to be referred to a psychologist or a psychiatrist for further assessment.
2. Exercise therapy should be the first line of treatment for adult asthmatic patients with comorbid mild or moderate depressive and anxiety of symptoms. The exercise therapy should be tailored to individual's need in terms of repetition, intensity and duration.
3. In a community-based rehabilitation including gymnasium, asthmatic patients should be encouraged to engage in a group or individual exercise programs to break the cycle of negative thoughts and hopelessness that feed into anxiety and depression.
4. Counselling therapy and educational therapy should be considered for adults asthmatic patients with elevated symptoms of anxiety and depression. It is paramount as well to monitor asthmatic patients with comorbid anxiety and depressive symptoms in routine clinical visits or telephone contacts, e.g. using the HAD scale.
5. If there is no improvement after the course of counselling therapy in depression or anxiety symptoms, further treatment can be considered to high intensity psychological interventions such as one-to-one CBT or group CBT. This depends on the patient's choice and provision of psychological therapy including CBT in local setting.
6. For those asthmatic patients with high level of depressive and anxiety symptoms with suicidal ideation should be offered antidepressants drug therapy preferably selective serotonin reuptake inhibitors because of their low side effects. In addition, follow-up visits, at least every 4 weeks, especially at the early stages are paramount in order to monitor the patient's adherence to treatment and progress and adverse events.

Conclusion

The nature of the relationship between asthma and mental health problems (whether it is bidirectional or not) is unknown. Therefore, future studies should explore the possible mechanisms, and triggering factors for the development of elevated anxiety and depressive symptoms are worthy endeavour.

Untreated comorbid anxiety and depression in adult patients with asthma may have devastating consequences, overwhelm the coping strategies of asthma patients and their caregivers and may increase healthcare utilization [39]. Future studies should examine the efficacy of PR, cognitive behavioural and antidepressants to treat anxiety and depression in well-controlled, randomized trials, with larger samples and long-term follow-up.

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Chapter 6
Depression and Anxiety in the Cystic Fibrosis Population

James Joseph Malatack, MD and Tara Lynn Barto, MD

Introduction

Cystic fibrosis (CF) is the most common fatal autosomal recessive disease affecting the Caucasian population [1] and is the result of a mutation found in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR gene encodes a protein which functions as a chloride channel in epithelial cell membranes in multiple organs [2]. The lack of appropriate quantity of functioning protein results in thick, tenacious secretions, most commonly affecting the respiratory and gastrointestinal systems. Phenotypically, CF causes progressive respiratory failure secondary to bronchiectasis, pancreatic insufficiency leading nutritional malabsorption and insulin-dependent diabetes mellitus, significant sinus disease, cirrhosis secondary to chronic cholestasis, and infertility [2].

Despite the common notion that CF is a rare disease, it has widespread impact affecting all racial and ethnic groups, but is most common among Caucasians with an incidence varying from 1 in 2000 to 1 in 3000 [3]. Overall, the incidence in the USA is estimated to be 1 in 3900 newborns, and approximately, 1000 new cases are diagnosed every year in the USA [3]. An estimated 30, 000 people in the USA have the disease [1]. According to the Cystic Fibrosis Foundation Patient Registry (CFFPR), before 1940 85% of CF patients died prior to age 2. However, since that time survival has significantly increased to a mean age of 16 years in 1970, 29 years in 1990, and 38 years of age in 2009 [1].

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The dramatic increase in life expectancy can be attributed to the evolution of new treatment options and better diagnostic tools, as a result of the discovery of the CFTR gene in 1989 by Francis Collins and his research team [4]. The mainstay of therapy includes chest physiotherapy, multiple inhaled treatments such as mucolytics and antibiotics, as well as many preprandial medications including insulin, vitamins, and pancreatic enzyme replacement therapy. The demanding nature of these treatment regimens, often requiring between 2 and 4 hours of time per day [5], can rob a patient and caretakers of their ability to form interpersonal relationships, develop careers, complete school. Frequently, these patients and families feel lack of control over their disease and they become a slave to the treatment burden. In addition to time-consuming daily regimens, most CF patients will require multiple inpatient stays for more intensive therapy. These isolating prolonged admissions can interrupt daily routines and slow maturation.

Recently, a healthy BMI has been linked to improved outcomes [3]; therefore, physicians have focused on improving BMI by recommending a high-protein, high-caloric diet. Unfortunately, this diet and BMI expectation in adolescent and young adult populations is associated with stigma of gluttony and being overweight often leading to non-adherence or stressful food-related situations.

These issues can lead to social isolation, poor job performance, and straining of relationships, all which may result in depression and anxiety. In addition, the nature of progressive respiratory failure can lead to significant anxiety-provoking symptoms such as shortness of breath and chest pain. CF patients and families from time of diagnosis are faced with the prospect of early mortality, which is difficult to overcome and lead a productive life.

Given the ever evolving and increasing effectiveness of therapies, resulting in patient longevity never before imagined, attention has recently been turned to the psychosocial aspect of the disease. Earlier studies focusing on anxiety and depression are sparse and statistically lacking. Now that the mean survival has moved beyond the teenage years, mental health and its impact on patients' ability to become productive members of society is becoming more important. This chapter will focus the recent robust but inconclusive literature on anxiety and depression in patients with CF.

Questionnaires

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) was developed in 1983 to identify signs and symptoms of anxiety and depressive disorders among patients outside of the psychiatric settings [6]. HADS is a 14-question tool with half the questions evaluating anxiety (HADS-A) and the other half depression (HADS-D). The HADS questionnaire purposely excludes all physical symptoms of anxiety and depression that could be the result of organic manifestations of the patient's chronic

disease. For example, the HADS does not ask about fatigue, which could be secondary to chronic disease or anxiety and depression. Therefore, the HADS gives a better evaluation of the true psychological state of a patient with medical disease.

HADS questions are scored 0–3 with a total score of 0–21 for anxiety and depression, respectively. In 2002, HADS was validated in nearly 750 studies. A score of 8/21 was determined to be a positive screen. Using this screening threshold resulted in the specificity and sensitivity of both HADS-A and HADS-D ranging between 0.75 and 0.90 [7]. The benefits of this tool are its ease of use, efficiency, and specificity to mental health, all very important characteristics of a screening tool. Importantly, it does not ask about suicidal ideation, which would require immediate intervention and thus is not ideal in a screening tool administered to a large population.

Minnesota Multiphasic Personality Inventory-2

The Minnesota Multiphasic Personality Inventory-2 (MMPI-2) was developed at the University of Minnesota in 1989. This questionnaire consists of 567 true/false items and is used to evaluate personality and emotional disorders. Scores of >70 are clinically abnormal [8].

Beck Depression Inventory

The Beck Depression Inventory is a 21-item questionnaire that assesses depression. Each item gives 4 statements options. Scores range 0–63. Score <10 is normal, score of 10–20 is marginally depressed, 20–30 is moderately depressed, 30–40 moderately severely depressed, and >40 reflects severe depression [8].

State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory is a 40-item questionnaire that determines both an individual's long-term susceptibility to anxiety as well as development of acute situational anxiety. Scores range 20–80. A higher score is indicative of anxiety predisposition [8].

Child Depression Inventory

The Child Depression Inventory (CDI) is a 27-item instrument that evaluates for depression in children less than 18 years. A score of 13 is consistent with clinically significant symptomatology [9].

Cystic Fibrosis Quality of Life Questionnaire

The CF Quality of Life (CFQOL) scale measures 52 items across 9 domains. This scale was created in with input from adolescents and adults with CF that highlighted important aspects of their quality of life. Domains include physical functioning, social interaction, treatment burden, chest symptoms, emotional functioning, future life goals, relationships, body image, and career goals. Scores of 50 or less within a domain indicate a negative response suggesting poor functioning in that domain [10, 11].

Questions of Life Satisfaction

The Question of Life satisfaction tool (FLZ) is a multidimensional measure of general and health-related life satisfaction in eight domains of daily life. Each domain is evaluated for both importance and satisfaction on a 5-point scale. Higher scores indicate better life satisfaction [12].

Prevalence of Psychopathology

It is well known that chronic diseases are associated with anxiety and depression. When looking at all chronic medical conditions, the lifetime risk of developing any psychiatric disease is 42.2% as opposed 33% of healthy controls [13]. When evaluating the prevalence of depression and anxiety specifically, between 15 and 27% of patients with inflammatory bowel disease carry a diagnosis compared to 5–12% in the general population [14]. Rheumatoid arthritis was found to have higher rates of mood disorders with approximately 40% of patients suffering from depression, anxiety or both [15]. Type 1 diabetes carries with it twice the risk of developing anxiety and depression than healthy controls [16]. Patients with autosomal polycystic kidney disease also have increased risk on anxiety and depression, which often worsens when kidney disease progresses to the point of requiring dialysis, which may indicate treatment burden affects psychosocial quality of life [17]. Given these statistics, it is not surprising that cystic fibrosis is associated with increased anxiety and depression.

Depression and anxiety are difficult to quantify within the CF population, largely stemming from the many diagnostic modalities used in the clinical studies. Each of the screening questionnaires has been validated in unique populations, with specific concurrent medical conditions and demographic profiles, which can be confounding factors. The diagnosis of depression or anxiety is traditionally screened for with questionnaires, of which there are several in existence. Unfortunately, there is not one such questionnaire that was specifically designed to evaluate the CF population.

Therefore, when reviewing the body of literature addressing mental health issues in CF, there is significant variability in the reported prevalence of depression and anxiety.

There are several studies that have attempted to quantify and characterize the mood disorders in CF. Yohannes et al. published a study in Manchester UK which evaluated 121 adult CF patients with a mean age of 30, using both the HADS and the Cystic Fibrosis Quality of Life (CF QOL) questionnaire [18]. Importantly, patients admitted to the hospital during the study and those who experienced an exacerbation were excluded. These exceptions may limit the true evaluation of CF patients with anxiety of depression given that the "sickest" patients were excluded. Twenty (17%) patients scored 8 or higher on HADS-D, and almost half those patients had positive scores in the HADS-A questionnaire. Scores of 8 and higher are considered indicative of depressive or anxiety symptoms [7]. In this study, depression had statistically significant association with impaired quality of life, decreased BMI, and low lung function [low forced expiration volume at 1 second (FEV1)]. Forty (33%) patients scored 8 or higher on HADS-A. Anxiety was statistically significantly associated with difficulty in interpersonal relationships, chest symptoms, older age, impaired quality of life, and hospital admissions. Lower quality of life scores were significantly associated with anxiety, depression, and hospital readmission. Interestingly enough, lower quality of life scores were not associated with age, sex, BMI, comorbidities, or decreased lung function.

While the prevalence of mood disorders in CF patient does seem to change based on geography, the patient characteristics associated with these diagnoses are fairly consistent. A study from Belgium found similar rates of anxiety and less depression than the previously described English study. Fifty-seven adults (mean age 26.7 years) with CF were screened for symptoms of anxiety and depression via the HADS questionnaire and completed the CFQOL. Anxiety symptoms were found in 30%, and depressive symptoms were found in 9% of patients. Patients with anxiety reported lower scores on vitality, emotional functioning, social, treatment burden, health perceptions, and respiratory symptoms domains of the CFQOL questionnaire. Those with depressive symptoms reported lower scores on emotional functioning, eating disturbances, and body image domains of the CFQOL. In this study, similar to the previous study described, patients who experienced an exacerbation were excluded [19].

A German study evaluated 670 CF patients, aged 12–64 years with the HADS questionnaire. In this study, 20.6% of the patients were found to have anxiety symptoms and 9.6% of patient had symptoms of depression. Compared to the general German population, only the adult CF patients had increased anxiety symptoms. This is unique when compared to prior studies in which all age groups of CF patients had significantly more depression than their age-matched control groups. This may be due to the relative stoic nature of the German culture. Younger patients reported fewer symptoms of anxiety and depression, and women were found to have higher rates of anxiety. Consistent across multiple studies, chest symptoms (hemoptysis/recent pneumothorax) and new diabetes diagnosis were associated with anxiety, while impaired lung function (FEV1 < 70%, < 40% even

stronger direct correlation), chest symptoms, and transplant listing status were associated with depression [20]. Depressed lung function (<70% FEV1 predicted) was associated with higher incidence of depression and anxiety as well as decreased quality of life. This decreased quality of life is still present when controlling for mood disorders, which emphasizes that there are several factors which play a role in the patient perception of a "good" life [19, 21].

Not all studies have found an increase in affective disorders in patients with CF. One study out of the USA compared 37 adult CF patients to 46 healthy controls and found no difference with respect to mental health, although CF patients did have a higher prevalence of sexual dissatisfaction if they were unmarried. Additionally, CF families were considered by the patient to be more accepting and supportive of changes in lifestyle and new activities [22]. Another small study, which evaluated 34 adults with CF and aimed to psychologically profile the patients by using multiple tests, found no significant level of psychopathology. Patients completed the Minnesota Multiphasic Personality Inventory-2, Beck Depression Inventory, and State-Trait Anxiety Inventory as part of the study. Interestingly, male sex was associated, but not found to be statistically significant, with higher scores of depression and anxiety. This is in contrast to prior studies in which woman were found to have higher levels of anxiety. Not unexpectedly, poor lung function was associated with anxiety and strong psychosocial support was inversely related to psychopathology [8]. The variability in the outcomes between studies highlights the complexity of study design and the likelihood that depression and anxiety are multifaceted mental health issues.

Parents and Caretakers

Parents and caretakers of patients with cystic fibrosis are also frequently affected by anxiety and depression. Parents of children with chronic illness need to cope with their child's mortality and frequently decreased ability to accomplish life goals and milestones, as well as the progression of disease and the financial burden placed on the family. It is thus quite understandable that parents of patients with chronic illness are more often anxious and depressed than parents of healthy children [23–25]. Depression is found more frequently in the mothers as opposed to fathers of CF patients, which is not surprising given the female predilection for depression and anxiety as well as the traditional maternal role as the primary caregiver [26].

A German study compared caregivers of patients with CF to the general population with respect to their symptoms of anxiety and depression. The study evaluated 650 parent/caregivers of 564 pediatric (0–17 years) patients with CF. The lung function of the patients measured from 15.7 to 138.7% (FEV1% predicted; mean 89.8%). Anxiety symptoms (HADS-A > 8, 37.2% in the caregivers compared to 18.9% in the general population) were found to be much more common than depression symptoms (HADS-D > 8, 28% in the caregivers compared to 21% in the general population). Life satisfaction scores (FLZ) were lower in the CF

caregiver population in several domains including leisure activities, general health, job situation, partnership/sexuality, and general life [12].

Caregiver psychopathology can have impact on both the mental and physical health outcomes of patients. For example, patients whose caregivers suffer from depressive symptoms are found to have worse adherence to enzymes as well as decreased BMI [27].

Adherence

While there is considerable evidence that CF patients have a higher incidence of affective disorders, the actual effect on a patient's organic disease process is still unclear. In patients with chronic diseases, depression is associated with a threefold increase in medical non-compliance [28]. Additional studies have confirmed that patients with chronic illness and depression have hindered medical compliance [29–31].

Specific data on the effects of CF psychopathology on medical adherence are sparse and contradicting. One recent study demonstrated no change in medical adherence in patients with depression compared to non-depressed CF patients, while anxiety may correlate with improved medical adherence [32]. Another study showed that depression in both patient and caregivers has been linked to have worsening compliance with pancreatic enzymes and consequently worsening BMI [26]. A third study found that depression in CF patients and/or parents led to poorer adherence to airway clearance among both school-age and young adult patients [33]. To date, there has been no large-scale definitive evaluation of medical adherence and psychopathology in CF although the literature in other chronic illnesses, combined with these few small-scale studies, indicate worse adherence in general to medical therapies in the setting of depression or anxiety, in either the patient or caregiver.

Vitamin D

There are multiple proposed reasons why patients with cystic fibrosis have higher rates of mood disorders, including higher rates of vitamin D deficiency. CF patients frequently have hypovitaminosis D as it is poorly absorbed through the gut due to pancreatic insufficiency. Vitamin D deficiency has been linked to depression [34–36]. This may be due to vitamin D's role in glucocorticoid signaling, melatonin synthesis, and regulation of catecholamines [37]. A recent study looked at 38 patients with CF, aged 7–17 years, with nearly all the patients on the standard vitamin D supplementation. The study found 59% of patients were vitamin D deficient and 28% were considered to have depression determined via the Children's Depression Index (CDI). Patients with vitamin D deficiency had

statistically significant higher rates of depression even when controlled for poor lung function. While this does not establish a causal relationship, there does seem to be an association between vitamin D deficiency and depression [9]. Future research will need to evaluate whether repletion of vitamin D will lead to improvement of depressive symptoms.

Treatment

Anxiety and depression can often be treated effectively in the general population. Generalized anxiety disorder has good response rates to both cognitive behavioral therapy (CBT) and medications (SSRIs, SNRIs, pregabalin) [38, 39]. Major depressive disorder generally has a good prognosis with treatment with CBT and/or medications [39, 40]. Unfortunately, there have been no studies to date that evaluate CF patients with mood disorders and their response to CBT or medications. While it may be theorized that CF patients should respond well to these known and tested therapies, the component of organic disease that is specific to CF may limit response. For example, while SSRIs may improve the patient's depressive symptoms, the anxiety caused by the shortness of breath due to cystic fibrosis-induced destruction of lung parenchyma would be unlikely to improve. As with vitamin D deficiency, future studies will need to be directed at response to CBT and medications in CF patients with mood disorders.

Non-cystic Fibrosis Bronchiectasis

Bronchiectasis is the term used to describe the dilated, scarred airways of the lung and is the hallmark lung pathology seen in cystic fibrosis. Bronchiectasis can be caused by a myriad of other causes, which leads to a population of patients with similar chest symptoms, requiring a similar pulmonary treatment profile, referred to as non-CF bronchiectasis patients. While their symptoms and treatments are similar, the etiologies of their disease are quite varied, leading to variable disease progression, and may or may not be associated with complicating conditions (e.g., diabetes, malnutrition). A 2002 study evaluating 111 patients with bronchiectasis found the prevalence of anxiety symptoms to be 17% and depressive symptoms to be 9% [41]. Another cross-sectional study looked at 93 adult patients with bronchiectasis and found that 20% had depression and 38% had anxiety symptoms [42]. The percentage of mood disorders in this population is very similar to those patients with CF.

Not unexpectedly, caretakers of these patients are also affected. A 2012 study looked at the parents of 69 children with bronchiectasis. The parents were evaluated for mental health and quality of life at baseline and during an exacerbation.

Parents were found to have poorer scores on questionnaires for both depression and quality of life during an exacerbation [43].

While there is even less literature on mood disorders in non-CF bronchiectasis than in the cystic fibrosis population, it seems that the prevalence is similar between the two disease processes. This is interesting, as non-CF bronchiectasis does not have the same mortality implications as CF, nor is it diagnosed early in life as commonly.

Conclusion

Chronic diseases are known to cause increased risk of psychological symptoms in both individuals with disease as well as their caretakers and families [13–17]. Not surprisingly, there is a similar association in patients with cystic fibrosis [18–22, 24–27]. While both depression and anxiety are more prevalent in the CF population, it is anxiety that is the driving force of the psychopathology [18–22]. Pulmonary symptoms, especially dyspnea and air hunger, play a major role in producing anxiety [18–22]. Furthermore, patients with CF must also learn to cope with abnormal body image, social stigma of cough, the time needed to complete treatment regimens, potential abnormalities of reproductive health, as well as their own mortality at a young age.

The CF care guidelines [44], while very extensive, do not address screening for depression and anxiety or recommend disease-specific treatment. Still, the largest review suggested that yearly depression and anxiety screening would be beneficial given the elevated prevalence in the CF population [23]. Depression and anxiety are very treatable as primary processes [38–40], although few studies evaluate depression and anxiety treatment in CF.

While the standard medication and behavioral therapies may or may not be equally as effective for the psychopathology in CF, the organic disease process (for example, decreased lung function causing dyspnea) will require a unique treatment approach. The scientific community recognizes anxiety and depression as an important issue in this population. Currently, a large multinational, multicenter study called The International Depression/Anxiety Epidemiologic Study (TIDES) is underway. TIDES study is a cross-sectional design, which looks at HADS and the Center of Epidemiology Studies Depression Scale (CES-D) in patients (12 years of age and older) with CF and the caretakers of those patients. The CES-D is a self-reporting question to help screen for depressive symptoms. Given the size and diversity of the population studied, the information gathered will be invaluable to the goal of finding risk factors for anxiety and depression as well as the utility of screening in the CF population. However, the study will not address treatment adherence or disease outcomes that may be associated with improved psychological health. These questions would provide a number of suitable objectives for future research endeavors.

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Chapter 7
End-Stage Lung Disease and Lung Transplantation

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Introduction

During the last decade and a half, lung transplantation has become an increasingly recognized and established intervention in the management of patients with a variety of end-stage pulmonary diseases such as chronic obstructive pulmonary disease, idiopathic interstitial pneumonia, cystic fibrosis and alpha-1 antiprotease deficiency-related emphysema [1, 2]. In spite of its benefits, a substantial proportion of lung transplant recipients experience symptoms of depression and anxiety that can negatively influence their ability to cope with the new organ, their adherence to rehabilitation, pharmacologic therapy and their overall quality of life [3]. Multiple studies have shown that individuals with end-stage lung disease that are listed to receive lung transplantation have substantially poor quality of life and that there is significant improvement in such, after lung transplantation. However, these studies have methodological limitations as well as limitations in the form of missing data, incomplete questionnaires and small sample sizes.

Coping with Chronic Respiratory Failure and End-Stage Lung Disease

Individuals with end-stage lung disease and lung transplant recipients often have significant psychosocial issues. End-stage lung disease poses an enormous challenge by way of emotional changes and an individual's ability to cope with progressive decline in lung function. Chronic hypoxemia, dyspnea and related physical

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restriction lead to common emotional and psychiatric disorders, particularly depression and anxiety. They are fairly common in individuals with end-stage lung disease who are potential candidates for lung transplantation [4]. An approximate 50% of individuals being screened for transplantation had a lifetime history of psychiatric illness [5]. Lack of hope for the future, poor energy, poor sleep and poor concentration are common in individuals with end-stage lung disease.

The limited literature available on the prevalence of psychiatric illness in individuals who are listed for lung transplantation shows increased rates of lifetime psychiatric illness compared with control populations, but similar rates when compared with other end-stage disease populations [6]. In addition to this, it is postulated that the respiratory symptoms and the psychiatric changes related to end-stage lung disease are most prevalent at night leading to significant sleep disruption. This in turn can worsen depression and anxiety. This vicious cycle combined with high levels of fatigue can significantly impair an individual's problem-solving and coping strategies, ultimately impacting overall quality of life [6].

Depression and Anxiety in End-Stage Lung Disease

The most common psychological responses to dyspnea secondary to chronic respiratory failure are mood disturbances, specifically depression and anxiety. More recent observations note that roughly 25% of individuals listed for lung transplantation met diagnostic criteria for at least one current mood or anxiety disorder [7]. Chacko et al. [8] reported that approximately 10% of individuals waiting for lung transplantation met criteria for a depressive syndrome and, overall, roughly 60% and 32% of them met criteria for a DSM-III-R Axis I and Axis II diagnoses, respectively. Clearly the prevalence of depression or anxiety in individuals with end-stage lung disease is at least higher than those noted in general population [9]. The symptoms of depressive or anxiety disorder can get worse along with the natural history of end-stage lung disease. It often is a result of subjective sensation of dyspnea, pain and the added stress that subjects upon active listing for lung transplantation, experience during the waiting period. The impact of depression on the overall survival rates cannot be taken lightly, particularly during the course of assessment of lung transplant candidacy. These individuals are often desperate to achieve an improved quality of life which often is not possible given the progressive decline toward end-stage lung disease. They would be glad, often, to trade quality to the length of life. Given the scarcity of the available lungs for transplantation, early identification of factors prior to transplant, as part of candidate selection, that contribute to a poor quality of life and a poor life expectancy following transplant would be of great benefit. Anxiety disorders including panic disorder seem to be associated more often in individuals with end-stage lung disease (advanced and chronic) compared to other solid organ transplant recipients [10]. It seems to continue through the peri-lung transplant period and after lung

transplantation as well, although at a lower intensity. One possible explanation might be the constant fear of impending doom and the serious debilitating symptoms and functional limitation these conditions impose on an individual.

Psychosomatic and Social Assessment for Lung Transplantation

The psychosomatic and social assessment is absolutely imperative as part of candidate selection for lung transplantation. It is perhaps most relevant to ascertain the relationship between the individual and his or her capacity to adhere to prescribed pharmacologic immunosuppressive regimen and medical follow-up. It is absolutely mandatory and a prerequisite that lung transplant recipients be on lifelong immunosuppression to preserve graft function. Non-adherence often leads to late acute lung allograft rejection episodes, graft loss and death. It is often assumed that transplant recipients, in general, represent a highly motivated group and that adherence rates would be high. Unfortunately, this does not seem to be the case. Overall, in solid organ transplant recipients, the non-adherence rates can vary from 20 to 50% [11, 12]. In a meta-analysis by Laederach-Hofmann et al. [13], lack of adherence to the prescribed immunosuppressive medication regimen was responsible for 25% of deaths after solid organ transplantation.

Most lung transplant programs as part of psychosomatic and social assessment during candidate selection strive toward a secure prediction of psychosocial adjustment and adherence. This can be accomplished by applying a rating instrument or a clinical tool that takes multiple factors into consideration. A detailed assessment of the pros and cons of various clinical rating tools is beyond the scope of this review. Two comprehensive clinical tools that are frequently used are the Transplant Evaluation Rating Scale (TERS) and the Psychosocial Assessment of Candidates for Transplant (PACT) [14, 15]. Both have reasonable internal consistency and seem to correlate fairly highly with each other as well.

In our lung and heart–lung transplant programs, we use the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) as a tool for psychosomatic and social evaluation of pre-transplant candidates [16]. Its strengths include the standardization of the evaluation process and its ability to identify subjects who are at risk of negative outcomes after the transplant, in order to allow for the development of interventions directed at improving an individual's candidacy.

In general, lung transplant recipients tend to use positive coping strategies rather than negative ones that seem to be less frequent [17]. Characteristics that identify personality problems or adjustment patterns detected by psychosocial screening can potentially assist with choosing interventions at the earliest possible window to decrease the levels of depression and anxiety, improve quality of life and assist individuals with end-stage lung disease to cope with multiple stressors including peri-lung transplant events.

Depression, Anxiety, Survival and Quality of Life After Lung Transplantation

Woodman et al. [18] compared the functional outcome of lung transplant recipients with and without history of a psychiatric ailment. They observed that a pre-transplant psychiatric diagnosis does not necessarily worsen survival following lung transplantation. Similar finding was reported by Squier et al. [19] who found that a diagnosis of depression before intervention is not an independent predictor of survival in the short term after lung transplantation. However, these findings have several limitations including a small sample size, and the fact that highly selected population that underwent a detailed psychosocial assessment prior to lung transplant listing was included. In addition, only short-term (1 year) survival rates were evaluated. This calls for further research with a larger sample size, representative of patients with end-stage lung disease for further clarification toward the longitudinal course and the long-term effects of depression on survival rates in this population. In the absence of evidence for the cumulative risk of depression among lung recipients, quality of life is suggested by some authors to assess the course of subjective well-being and psychosocial functioning [20].

Many studies as well as the International Society of Heart and Lung Transplantation (ISHLT) registry have shown that successful lung transplantation confers both a survival benefit and an improvement in quality of life as a benefit as well. The former is particularly true with certain end-stage lung diseases, particularly the end-stage, restrictive and fibrotic group of lung diseases (Figs. 7.1 and 7.2 [1, 21]). In addition, the ISHLT 2012 data (Fig. 7.2) also notes that over 85% of lung transplant recipients show no activity limitation and that this level of independence with daily activities is retained at 1, 3 and 5 years after lung transplantation. Studies have reported that lung transplant recipients have better overall general, physical and psychological health compared to those that are pre-lung transplant, with end-stage lung disease [3, 22–24]. This improvement in quality of life leads to decrease in the prevalence and intensity of symptoms of depression, starting within the first few months after lung transplantation, and seems to be sustained for the next 1–3 years [3, 24]. It almost drops to the level comparable to those of the general population [3, 24]. A majority of individuals after successful lung transplantation acknowledge ‘the privilege of receiving a second chance at life and a successful extension of it’ compared to severely limiting and life-threatening end-stage lung disease. They also report less symptoms related to depression and anxiety. Although it has been proposed that the psychological issues could potentially be ‘lung disease specific,’ some of the published data do not seem to favor this notion. Vermeulen et al. compared the effect of lung transplantation in individu als with cystic fibrosis with other most commonly transplanted end-stage lung diseases such as chronic obstructive pulmonary disease (COPD), idiopathic

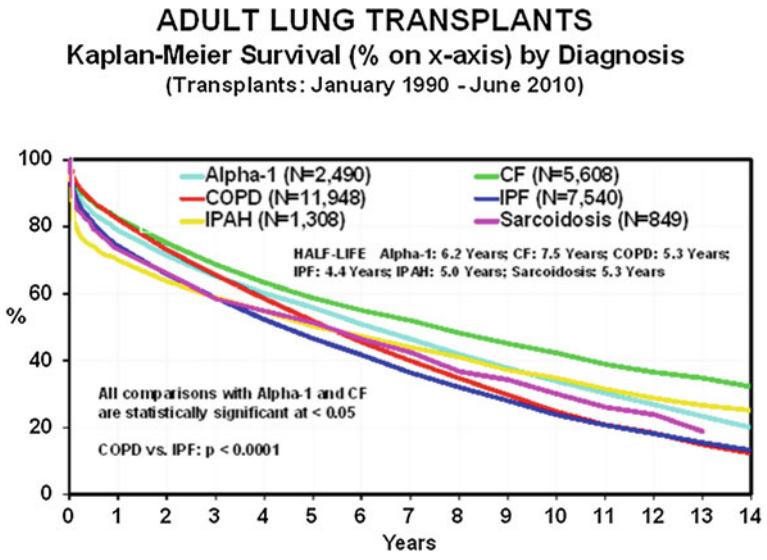

Fig. 7.1 Adult lung transplants (Kaplan–Meier Survival (% on x-axis)) by diagnosis (transplants: January 1990–June 2010). Reproduced from http://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry, journal of heart Lung Transplant. 2012 October; 31(10): 1045–1095, with permission

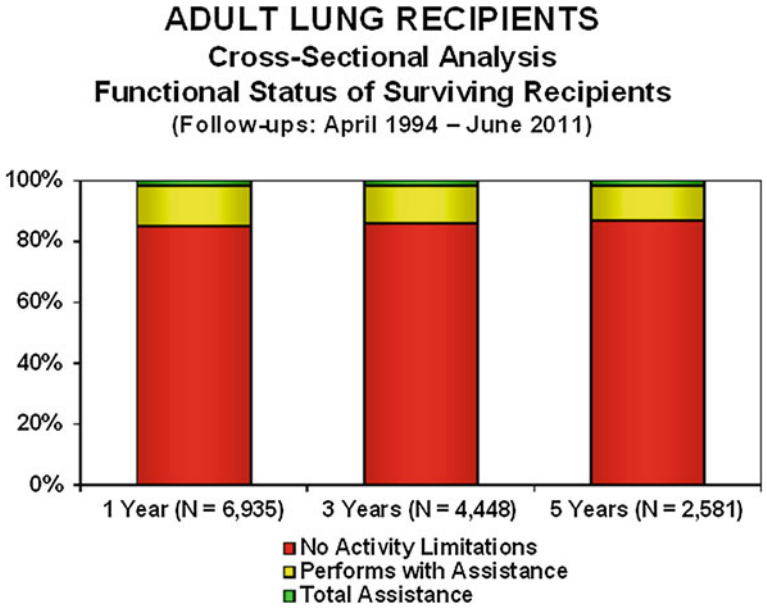

Fig. 7.2 Adult lung recipients. Cross-sectional analysis—functional status of surviving recipients (follow-ups: April 1994–June 2011). Reproduced from http://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry, Journal Heart Lung Transplant. 2012 October; 31(10): 1045–1095, with permission

pulmonary fibros is (IPF) and alpha-1 antiprotease deficiency-related emphysema. They found no significant differences with respect to depression and anxiety in the short term, following lung transplantation [24].

Effect of Immunosuppressive Medications

Lung transplant recipients are maintained on lifelong immunosuppressive regimen and prophylaxis against opportunistic infections. They certainly experience adverse effects from these medications that tend to contribute to poor perceived quality of life. This in turn can contribute to depression and anxiety [22]. The effect of high dose glucocorticoids (an essential component, early in the course of lung transplantation) on mood and coping skills, with increase in depression and anxiety cannot be understated [25–27]. In addition to this, Tacrolimus and Cyclosporine (calcineurin inhibitors, the core component of immunosuppressive regimen after lung transplantation) can cause insomnia, restlessness and tremor [28–31]. Combined, these adverse effects can certainly interfere with coping skills and impact the quality of life. Additionally, difficulties encountered while navigating loss of control and dependence on caregivers (for activities of daily living), family and friends can potentially lead to significant distress and overall mood changes.

Adherence to Medical Regimen and Post-lung Transplant Clinical Monitoring

It is imperative that lung transplant recipients receive life-long immunosuppression to prevent lung allograft rejection. It does add a significant burden to the recipient and could potentially lead to non-adherence. There are published data in kidney, heart and liver transplant recipients that medical non-adherence is the single most important risk factor for acute allograft rejection and graft loss. In heart and kidney transplant recipients, pre-transplant adherence was identified as a significant predictor of survival after transplantation [32–40]. Moreover, in heart transplant recipients, non-adherence to medical regimen during the first year after transplantation increased the risk of acute cardiac allograft rejection by over fourfold [37]. This finding highlights the importance of urging all solid organ transplant recipients to remain adherent to the prescribed medication regimen. It was reported that adherence to medical regimen worsens over time after heart transplantation [41]. A plethora of psychosocial factors, stressors and physical complications have been empirically cited as potential factors that can contribute to poor quality of life that in turn can lead to depression, anxiety and poor adherence to medical regimen and clinical monitoring in lung transplant recipients (Table 7.1 [42–48]). In addition to some of the above identified factors, other reported risk factors for

Table 7.1 Psychosocial factors, stressors and physical complications [42–48]

• Prior psychiatric illness
• Poor self-esteem
• Time spent on the waiting list
• Living and having to cope with a terminal illness
• Needing an organ transplant
• Worrying family members
• Prolonged hospitalization
• Fear of death
• Stress related to the use of a beeper
• Deteriorating physical health
• Loss of control (a low sense of independence, high level of worry and difficulty with activities of daily life)
• Post-transplant obesity
• Loss of employment
• Sexual dysfunction
• Intercurrent illnesses such as infections
• Acute lung allograft rejection
• Readmission or hospitalization after successful discharge
• Chronic lung allograft rejection (bronchiolitis obliterans syndrome/BOS, Restrictive Allograft Dysfunction)
• Immunosuppressive medications particularly prednisone
• Poor caregiver or family support

non-adherence include lower age particularly adolescents, male gender, higher educational level, longer period after lung transplantation and depression. Bosma et al. reported 7.7% rate of non-adherence to immunosuppressive therapy in recipients, one year after lung transplantation. They note that recipients less than 1 year after lung transplantation were not included due to logistic limitations. In their study they noted that age, especially adolescents and adults with decreased ability to care for self appeared to be more at risk of non-adherence [49].

Psychological Interventions

Following lung transplantation, recipients often experience depression and anxiety and associated perceived poor health-related quality of life. There is a high risk that this ultimately could lead to non-adherence to medical regimen and clinical monitoring with a risk of acute lung allograft rejection and adverse short-term and long-term outcomes. In addition, lung transplant recipients are already on numerous medications making addition of medications to treat depression and anxiety more difficult. It comes at an added risk of serious drug to drug interactions as well (Table 7.2 [50, 51]).

Table 7.2 Antidepressant medications used in the treatment of depression after lung transplantation and potential interactions with immunosuppressive agents [50, 51]

Medications	Class	[a]Interactions with rejection meds
Fluoxetine	SSRI	Increased level
Paroxetine	SSRI	Increased level
Sertraline	SSRI	Increased level
Trazodone	SSRI	Increased level
Fluvoxamine	SSRI	Increased level
Nefazodone	SSRI, NE & DOPAMINE uptake inhibition	Increased level
Venlafaxine	SSRI, NE & DOPAMINE uptake inhibition	Increased level
Bupropion	SSRI, NE & DOPAMINE uptake inhibition	Increased level
Mirtazapine	Atypical tetracyclic, increases NE and DOPAMINE release by pre-synaptic (central) alpha-2 antagonism	Increased level
Citalopram	SSRI	Increased level

[a]By inhibition of CYP3A4 isoenzyme system, elevation of cyclosporine level can result when these agents and tricyclic antidepressants are used. Although rare, it can happen when used in conjunction with tacrolimus as well. Hence, it is always recommended to exercise caution and carefully monitor the drug levels (calcineurin inhibitors)

A number of strategies to treat depression and anxiety after lung transplantation were utilized. Broadly, they can be divided into non-pharmacologic and pharmacologic interventions. Non-pharmacologic strategies include cognitive psychotherapy, family or group therapies and complimentary therapies such as relaxation techniques, mind–body therapies, prayer and support groups [20, 52]. They could potentially help with the coping process and a perception of better quality of life. Pharmacologic therapy broadly includes antidepressant and anxiolytic medications.

Tricyclic antidepressants (TCAs) have a plethora of adverse effects and drug to drug interactions, making them a less appealing choice to use in lung transplant recipients. Selective serotonin reuptake inhibitors (SSRIs) and new-generation antidepressants such as mirtazapine are the first-line medications of choice to treat symptoms of depression. Their favorable adverse effect profile with fewer drug to drug interactions particularly with immunosuppressive medications make them a very appealing first line of choice (Table 7.1). Unfortunately they do cause inhibition of hepatic CYP450 enzyme system. Caution should be exercised when SSRIs are initiated. They increase the levels of immunosuppressive medications particularly the calcineurin inhibitors (CNIs), namely cyclosporine and tacrolimus, more so with the former. Hence, it is highly recommended that CNI drug levels are periodically monitored and necessary adjustment to the dosage made to maintain optimum levels and avoid potentially life-threatening adverse effects and toxicities. Caution should be exercised with careful consideration toward other drug-to-drug interactions. An important example is prolongation of Q-T interval which needs to be closely monitored with frequent ECG testing.

Anxiety and insomnia can be crippling in individuals with end-stage lung disease and in lung transplant recipients. Although benzodiazepines are commonly used for these symptoms, they can cause respiratory depression and blunt the arousal response to hypercapnia even at therapeutic doses in a few individuals [4, 53]. Mirtazapine is promising and has a dual mode of action without the adverse effects of benzodiazepines and seems beneficial for depression and anxiety [54].

Summary

Individuals with end-stage lung disease and lung transplant recipients are a heterogeneous group. These conditions impose significant psychosomatic limitation by way of depression and anxiety. Evidence clearly indicates that depression and anxiety are the most common psychological sequelae of end-stage lung disease and complications after lung transplantation. Despite such limitations, when successful, lung transplantation results in survival benefit as well as quality of life benefit. It also yields in significant improvements in physical and psychological health. Clinical screening tools are an essential integral part of pre-lung transplant psychosocial assessment to assist in early identification of stressors and risk factors in individuals with potential for poor coping skills and medical non-adherence as they have a negative impact on post-lung transplant quality of life and outcomes. Heightened vigilance for symptoms and signs of depression and anxiety disorders in all individuals with end-stage lung disease and lung transplant recipients is warranted. Successful lung transplant centers have dedicated medical social workers, psychologists and psychiatrists as essential, integral members of a multidisciplinary lung transplant team. Such system would assist in screening, identification and intervention for depression, anxiety and high-risk behavior that have a negative impact on the quality of life and clinical outcomes after lung transplantation. There is a definite role for psychological (non-pharmacological and pharmacological) interventions in individuals with end-stage lung disease and after lung transplantation, at the earliest possible window, to alleviate symptoms related to depression and anxiety and to assist with coping and improve overall quality of life and outcomes after lung transplantation.

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Chapter 8
Sleep-Disordered Breathing and Mental Illness

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Introduction

> Sleep that knits up the ravelled sleave of care, The death of each day's life, sore labour's bath, Balm of hurt minds, great Nature's second course, Chief nourisher in life's feast.
>
> Shakespeare, Macbeth

Magnitude and Scope of the Problem

Mental disturbance is extremely common among those who suffer from sleep disorders. Most psychiatric patients have sleep complaints, and a primary sleep disorder frequently also results in neuropsychiatric complications. Up to 2/3rd of patients who present to a sleep disorders center report an episode of depression within the previous 5 years, and one quarter described themselves as depressed at presentation [1].

Chronic sleep loss and sleep disorders impose an immense public health burden, and awareness among the general public and healthcare professionals remains low.

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It is estimated that 50–70 million Americans suffer from a chronic disorder of sleep and wakefulness, hindering daily functioning and adversely affecting health. Insomnia is the most common sleep disorder, followed by sleep apnea and restless legs syndrome (RLS). Obstructive sleep apnea (OSA) is by far the most common form of sleep-disordered breathing, in which a person frequently stops breathing during his or her sleep. It results from an obstruction of the upper airway during sleep that occurs because of inadequate motor tone of the tongue and/or airway dilator muscles. More specifically, it is characterized by 'hypopneas' (decreases in breathing during sleep) or 'apneas' (actual pauses in breathing). Pauses in breathing during sleep of at least 10 seconds with obstruction of oronasal airflow despite continuous chest and abdominal movements are referred to as 'Obstructive Apneas' and are associated with a decrease in oxygen saturation and/or arousals from sleep [2]. Many patients with obstructive OSA also have central apneic episodes in which breathing stops temporarily but without any airway blockage or respiratory effort. Both kinds of episodes can cause harmful reductions in the level of oxygen in the blood.

OSA is a common sleep disorder prevalent in at least 2–4% of the adult population. The prevalence of OSA is increasing along with the epidemic of obesity in the USA. Risk factors for OSA include obesity, craniofacial abnormalities, upper airway abnormalities, heredity, smoking and nasal congestion. The core features of OSA include nocturnal hypoxemia, hypercapnia and sleep fragmentation with resultant excessive daytime sleepiness, mood problems, poor neurocognitive performance and potentially serious organ system dysfunction including a variety of adverse cardiovascular and metabolic effects. Some studies have suggested executive dysfunction in OSA patients, thought to be related to prefrontal lobe dysfunction caused by intermittent hypoxia. All of these conditions can seriously contribute to decrements in a patient's quality of life [2].

Mental disorders are highly prevalent in the general population and even more so among individuals with sleep disorders. Mood and anxiety disorders are associated with high rates of insomnia. Similarly, for many patients with sleep complaints, mental illnesses like depression and anxiety play an important role in their sleep complaints. Medications used for the treatment of mental illnesses can also play a significant role in the genesis or exacerbation of sleep complaint [3]. People with severe mental illness generally die sooner (in many cases as much as 25 years or more) compared with the general population, and this is primarily due to the high prevalence of physical illness, such as cardiovascular disease, rather than suicide. OSA plays a critical role in causing and exacerbating medical illnesses in these individuals. Thus, treating the general health of people with severe mental illness (including effective treatment of illnesses like OSA) is crucial [4].

Sleep disturbances are common in both mood and anxiety disorders. Some believe that there may be a bidirectional relationship between sleep disturbance and mental illnesses [3].

Some of the twentieth century's most devastating human and environmental health disasters have been attributed directly or indirectly to sleep loss, excessive sleepiness and fatigue-related performance failures including the tragedy at the Union Carbide chemical plant in Bhopal, India; the nuclear reactor meltdowns at

Three Mile Island and Chernobyl; and the grounding of the Exxon Valdez oil tanker.

The Clinical Significance of Obstructive Sleep Apnea

In addition to the considerable overlap between OSA and psychiatric illness, primarily depression and anxiety (addressed in the next section), OSA is also comorbid with multiple medical conditions. Research in the last 15 years has debunked the notion that chronic sleep deprivation has no health consequences apart from excessive daytime sleepiness [5]. Current research suggests that chronic sleep loss (less than 7 h a night) including sleep loss secondary to OSA has wide-ranging effects on the cardiovascular, endocrine, immune and nervous systems, including the following:

- Obesity in adults and children
- Diabetes and impaired glucose tolerance
- Cardiovascular disease and hypertension.

This is in addition to the negative effects of sleep loss on mental health which include anxiety symptoms, depressed mood and alcohol use.

Sleep Loss and Obesity

Obesity (defined as having a Body Mass Index (BMI) equal to or greater than 30 is now a major public health problem in developed nations and developing nations such as China and India are not far behind. It is well established that obesity is linked to multiple medical problems including increased risk of diabetes, heart disease, arthritis and cancer. Chronic sleep deprivation (less than 7 h per night) is one risk factor for obesity that has received increased attention in the last few years. The reduction in average sleep hours over the last three to four decades (with the widespread availability of television, video, computers, the internet, etc., as well as a rapid increase in the incidence of shift work) has coincided with the increase in the prevalence of obesity leading researchers to suspect a link between the two.

A recent study reported that the sleep duration of the average American adult has decreased to an average 6 h 40 min (weekdays/7 h 25 min-weekends) from 8.5 h in 1960 [6]. Chronic sleep loss can have a negative effect on appetite via two hormones that play a major role in appetite regulation: leptin, a satiety hormone produced by adipocytes and ghrelin, an appetite stimulant released by stomach cells. These chemicals exert opposite effects on appetite. Leptin levels are lower in the morning and rise gradually throughout the day. Leptin inhibits hunger during the overnight fast. Ghrelin levels decline immediately after meals and then rise

again after a few hours. Sleep exerts an inhibitory effect on ghrelin. In addition, sleep restriction leads to an increase in calorie consumption likely secondary to continued energy expenditure due to physical activity [7]. Obesity is one of the primary and more modifiable risk factors for development of OSA.

A number of studies suggest that reducing obesity will likely benefit sleep disorders, and treating sleep deprivation and sleep disorders may benefit individuals with obesity [7].

Sleep Loss and Impaired Glucose Tolerance

The link between obesity and diabetes is well established as is their long-term morbidity and mortality [8]. Recent studies have also pointed out the link between obesity, diabetes and chronic sleep deprivation [9]. It can be shown in healthy people that short-term sleep deprivation causes impaired glucose tolerance; thus, sleep might be essential for metabolic homeostasis. In addition, evidence is available that obstructive sleep apnea syndrome, narcolepsy and restless legs syndrome are all associated with impaired glucose tolerance or an increased incidence of diabetes [10, 11].

This association between impaired glucose tolerance and diabetes may partially explain the relationship between sleep loss and cardiovascular disease as discussed next.

Sleep Deprivation and Cardiovascular Disease

Several large epidemiological studies have documented the association between sleep loss and cardiovascular illness including myocardial infarction and possibly stroke. For sleep disorders such as OSA, the association is particularly strong since OSA has been proven to cause systemic hypertension, possibly myocardial infarction, congestive heart failure and stroke [12]. Several potential mechanisms for these phenomena have been suggested including autonomic, metabolic and inflammatory factors and oxidative stress. OSA results in sustained breathing efforts during pharyngeal collapse which leads to markedly negative intrathoracic pressure, hypoxemia and arousal from sleep. This leads to increased transmural cardiac pressure and ventricular afterload. Additionally, hypoxemia and repeated arousals from sleep lead to sympathetic surges increasing blood pressure and heart rate. Recurrent hypoxemia/reoxygenation cycles resemble ischemic events yielding reactive oxygen species such as peroxides and free radicals which promote atherosclerosis via a proinflammatory environment. Institution of CPAP (continuous positive airway pressure) can minimize or reverse many of these phenomena [13].

Clinical Observations About Sleep-Disordered Breathing and Psychiatric Illness

In the authors' experience, patients with psychiatric conditions are more vulnerable to develop OSA. There are several likely reasons for this. First of all patients with psychiatric disorders like schizophrenia and mood disorders are more likely to be obese which puts them at risk of development of metabolic syndromes. Secondly, many antipsychotic medications, antidepressants and mood stabilizers increase the risk of weight gain. In addition, depressed patients have low motivation to exercise and lead a healthy lifestyle, putting them at further risk of obesity and thus OSA.

Not all mental health clinicians are familiar with sleep-disordered breathing's comorbidity with psychiatric diseases, which poses an impediment in the care of these patients. Excessive daytime sleepiness is often attributed to either the illness or side effect of multiple medications patients are on.

Often patients with chronic psychiatric disorders have irregular sleep wake schedules, which confuses the clinical picture. Mental health clinicians might not pay attention to excessive daytime sleepiness as they feel that the symptoms are due to insomnia or medications.

There are studies suggesting that patients with depression and anxiety disorders including PTSD have poor adherence to CPAP [14]. Patients suffering from post-traumatic stress disorder (PTSD) are often claustrophobic and tend to prefer oral appliances. Systematic desensitization might help reduce feelings of anxiety with these patients. Educational and interactive groups focusing on adherence of CPAP might improve the use of CPAP as patients learn from their peers and see how others have been able to overcome non-adherence and benefitted from CPAP use.

The Prevalence of Depression and Anxiety in Obstructive Sleep Apnea

Population and Community Prevalence

Studies specifically designed to evaluate the prevalence of comorbid OSA and depression are few in number [15]. A recent large European survey (n = 18,980) reported a prevalence of major depressive disorder of 17% in patients with OSA or a sleep-related breathing disorder, while the prevalence for the whole sample was 4.3% [16]. In an even larger Veterans sample, this prevalence was found to be 21.8% in patients with OSA and only 9% in non-apneics [17].

This appears credible since the background prevalence of depression among people without OSA in these large-scale studies is consistent with earlier findings of 3–5% in community settings and 5–10% in primary care in the USA.

Older studies have reported higher rates of affective disorders in OSA (some up to 45%) and the risk seemed to rise in patients who were sleepier during the day

[18]. Those studies also found higher depression scores in patients with more severe OSA as indicated by a higher Apnea–Hypopnea Index (AHI).

Other smaller studies of severe OSA have reported very high prevalence of depression (in one study around 63%) [19]. It is impossible to draw any causal inferences from these data especially since the screening and diagnosis of depression in these studies are based on checklists and rating scales instead of in-depth clinical interview. Some of the overlapping symptoms of OSA and depression such as fatigue, decreased concentration, irritability and weight gain may confound the diagnosis.

An association between OSA and anxiety has also been documented. Data from the large Veterans study referenced above reveals a strong association between diagnosed sleep apnea and anxiety with 16.7% of OSA patients having comorbid anxiety and 11.9% with comorbid Posttraumatic stress disorder. Other studies have reported a relationship between nocturnal panic attacks and OSA [20].

Similarly, sleep problems are a central feature of PTSD, and this study strongly supports an association between sleep apnea and PTSD. Some authors have suggested that an arousal-based mechanism can promote the development of OSA after posttraumatic stress. There have been case reports and case series in which CPAP treatment of OSA improved insomnia, nightmares and PTSD symptoms [14].

Rates of Depression in Clinical Populations

Prevalence studies looking at people entering sleep clinics that were then diagnosed with OSA have shown high rates of depressive symptoms. One study found 41% of 167 Dutch sleep clinic referrals diagnosed with OSA according to American Sleep Disorders Association classification had a Beck Depression Inventory (BDI) score of 10 or more, indicating probable depression [21]. In a US study, sleep clinic depression rates among 406 people diagnosed with OSA were 30% overall (38% for women and 26% for men) [22].

Random selection of 130 women with ‘documented breathing disorders’ from a Canadian OSA clinical database showed 21% with a self-reported previous diagnosis of depression compared with 7% of 130 matched men from the same database [23].

Some variation in rates is to be expected with different clinical populations from different communities or when using different measures for depression. However, all of these studies report high rates of depression or depressive symptoms in people with OSA specifically women. Most of these studies, though, were not designed as prevalence studies. Therefore, this range is indicative of rates of depression in small clinical samples using variable inclusion/exclusion criteria. They cannot be generalized to people with OSA in populations nor can they be said to be indicative of the usual rates of depression in clinical OSA populations.

Obstructive Sleep Apnea and Mental Illness

OSA and Major Depression

Numerous studies have documented that OSA and depressive disorder are comorbid although some studies have questioned this correlation. There is a complex correlation between OSA and depression since there is considerable overlap between symptoms. The 'core' symptoms of OSA (such as snoring, snort arousals and witnessed apneas) differ clearly from some of the core symptoms of depression (such as sadness, anhedonia, guilt and agitation). However, there are a large number of symptoms common to both illness including fatigue, daytime sleepiness, poor concentration, irritability and weight gain. It is thus unclear whether depression is a primary consequence of OSA or whether some of these secondary symptoms of OSA such as sleepiness, sleep problems, irritability and social withdrawal manifest as a depressive syndrome. Current recommendations are that a mood disorder should be considered secondary to OSA and treated accordingly [24].

OSA and Anxiety

OSA has also been linked to anxiety and nocturnal panic attacks although the association between anxiety and OSA is not as well established as with depressive illness. Frequent awakenings due to choking from breathing cessations may play a role in the development of anxiety in OSA although this association is unproven. Studies have shown a correlation between anxiety disorders and one of the core symptoms of OSA, excessive daytime sleepiness (EDS) [25].

It has been suggested that anxiety may precede and potentially cause symptoms of EDS by contributing to insomnia and other sleep disturbances. This can be partially explained by the fact that anxiety disorders and the sleep wake cycle are regulated by several common neurotransmitters (e.g., Serotonin, γ-aminobutyric acid and neuropeptide Y). In a recent study, Rajesh et al. demonstrated MRI evidence of tissue injury in anxious patients with OSA versus patients with OSA but no anxiety [26]. This occurred in brain areas regulating emotion, and there was evidence indicating that many of these regions lay outside areas normally affected by OSA alone. This suggested additional injurious processes in anxious OSA subjects.

There is also an association between a family history of phobic disorders and EDS [24] as well as anxiety and chronic fatigue [27], another core symptom of OSA. Anxiety disorders are both highly prevalent and eminently treatable; therefore, these associations might have important clinical implications. In addition, OSA is highly prevalent in combat veterans with posttraumatic stress disorder who complain of being overly vigilant at night, nightmares, frequent awakenings and non-restorative sleep [28].

It is difficult to establish a clear correlation between sleep-disordered breathing and depression and anxiety symptoms. Lack of demonstrated relationship between OSA and psychiatric disorders does not necessarily mean there is no link between these conditions.

In most studies, there is lack of consistency with diagnostic criteria for OSA and for depression and anxiety. Most studies used clinical scales rather than diagnostic interviews to diagnose depression or anxiety. Most scales used for depression have sleep-related questions, either about hypersomnia or insomnia. Some authors suggested that questionnaires focusing on core symptoms of depression, like anhedonia or sadness, should be used in these studies [29].

In addition, confounding factors such as obesity, hypertension, diabetes and cardiovascular disease may impact the relationship between OSA and depression [30]. Both depression and OSA have independently been shown to be associated with metabolic syndrome and poor cardiovascular outcomes [31].

Studies suggesting a positive correlation between OSA and depression are summarized in Table 8.1, and studies suggesting no relationship between OSA and depression are summarized in Table 8.2.

Mechanisms

Pathophysiological Relationships

Sleep fragmentation and hypoxias a cause of depression.

The two major pathological events that occur in association in OSA with upper airway obstruction are: (1) fragmentation of normal sleep because of 'micro-arousals' occurring due to recurrent apneas and hypopneas leading to (2) recurrent, intermittent hypoxemia causing diminished saturation of oxyhemoglobin. These then lead to reduced daytime wakefulness, impaired cognitive function and low mood. Sleep fragmentation has been hypothesized as the principal cause of excessive daytime sleepiness (EDS) in OSA and patients with EDS and OSA are more likely to be depressed than patients with OSA without EDS [32].

Animal studies suggest that recurrent, intermittent hypoxemia, a central feature of OSA, is associated with a dose-dependent cell loss in the areas rich in noradrenergic and dopaminergic pathways important for both sleep/wake and mood regulation including the hippocampus and cortex. Concomitant depression can worsen neuronal injury accompanying OSA. Effective treatment of OSA with continuous positive airway pressure (CPAP) treatment leads to neuronal regeneration evidenced by gray matter volume increase in the hippocampus and frontal cortex volume [33]. This results in improvement in memory, attention and executive functions. Antidepressants have been shown to cause similar effects (increase in hippocampus volume via neurogenesis) [34].

Table 8.1 Studies suggesting a positive correlation

	Author/date	Population	Depression measures	OSA measures	Conclusions
Cross-sectional study	Enright/1996	5201 community sample of 65 year or older	CES-D	Self-reported Partner observed	Association in women, not in men
	Smith/2002	Records of 773 pts with OSA matched with controls	Physician diagnosis	Physician diagnosis	OSA pts OR of 1.4 past depression
	Aloia/2005	Sleep clinic sample of 93	BDI	RDI	Relationship of RDI and BDI total score and BDI somatic dimension. Independent relationship b/w RDI and somatic dimension for men
	Farney/2004	Records of >200,000 patients	Rx of antidepressant meds	Physician diagnosis	Likelihood of having OSA increased in depression
Cohort studies	Peppard/2006	1408 community patients (788 men)	Modified Zung depression scale or use of an antidepressant	PSG	1.8 odds ratio of developing depression in a 4-year interval as OSA develops or worsens. Dose–response relationship between severity of OSA and depression

Adapted from Harris et al. [15], with permission of Elsevier

OSA obstructive sleep apnea; *RDI* respiratory disturbance index; *CES-D* Clinical Epidemiological Scale for Depression; *BDI* Beck Depression Inventory; *SCL-90* Symptom Checklist-90; *HAD-D* Hospital Anxiety and Depression Scale; *SIGH-SAD-SR* Hamilton Depression Rating Scale-Seasonal Affective Disorders Self-Rating Scale

Table 8.2 Studies suggesting no correlation

First author/date	Study population	Depression measure	OSA measure	Conclusion
Kripke/1997	Community sample of 335	CES-D or items from SIGH-SAD-SR	Desaturations	No relationship
Pillar/1998	2271 referrals to a sleep clinic	SCL-90	RDI	No consistent relationship
Sforza/2002	44 OSA, 16 snorers	HAD-D	AHI, mean low oxygen saturation	No correlation b/w AHI and HAD-D, but with low O_2 sats

Adapted from Harris et al. [15], with permission of Elsevier
OSA obstructive sleep apnea; *RDI* respiratory disturbance index; *CES-D* Clinical Epidemiological Scale for Depression; *BDI* Beck Depression Inventory; *SCL-90* Symptom Checklist-90; *HAD-D* Hospital Anxiety and Depression Scale; *SIGH-SAD-SR* Hamilton Depression Rating Scale-Seasonal Affective Disorders Self-Rating Scale; *AHI* Apnea–Hypopnea Index

Neurotransmitter Disturbances

Obstructive sleep apnea is associated with elevated levels of the cytokines interleukin-6 (IL-6) and tumor necrosis factor (TNF). It has been hypothesized that these compounds are mediators of daytime sleepiness since administration of a tumor necrosis factor antagonist has been shown to dramatically reduce the level of daytime sleepiness in patients with OSA [35].

A vast body of literature has also documented the close association between major depression and the inflammatory immune response involving the proinflammatory cytokines IL-1, IL-6 and interferon [36]. While none of the studies are confirmatory for causation, they do suggest shared pathways between these conditions.

Further, obesity, particularly visceral obesity (a known risk factor for OSA), is also associated with an elevation in these cytokines [37].

Patients with OSA while awake are able to 'prop open' the upper airway through activation of the upper airway dilator muscles; when asleep, however, the neurochemical 'tonic' stimulation to upper airway motoneurons is lost as is muscle tone, resulting in pharyngeal collapse [38]. Abnormalities in central and peripheral neurotransmission of **Serotonin** have been implicated as a potential cause of major depression. It is now established that during wakefulness Serotonin, most probably acting through 5-HT2A receptors, provides a tonic excitatory input to hypoglossal motor neurons innervating the genioglossus and other upper airway dilating muscles. It is hypothesized that withdrawal of this serotonergic input during sleep might predispose to airway obstruction in the form of apnea or hypopnea [38, 39]. If we conceptualize a central pathology in OSA as easy upper airway collapsibility during

sleep, then anything decreasing the activation of upper airway dilator muscles during sleep can potentially cause the disorder. The activation of Serotonin receptors innervating the genioglossus and other upper airway dilator muscles, particularly 5-HT2A receptors, is excitatory. The release of Serotonin from the raphe neurons steadily declines with the transition from wakefulness to NREM sleep and is minimal during REM sleep. Thus, loss of 'tonic' serotonergic activity is one potential basis for the reduced upper airway muscle activation and increased collapsibility of the upper airway characteristic of OSA [38, 39]. However, this pathway is extremely complex, with multiple receptor subtypes, and there may be other pathways shared with other neurotransmitters.

Norepinephrine has several similarities with Serotonin as a neuromodulator of motoneuronal function although studies suggest that its role is complementary [38]. Hypoxia secondary to OSA also alters motoneuronal and extracellular levels of the purines **Adenosine and ATP**, specifically reducing ATP and increasing Adenosine. Adenosine injected into the hypoglossal nucleus suppresses hypoglossal motoneuronal activity. This association needs to be explored further [38].

A similar inhibition of hypoglossal nerve activity is observed with **Acetylcholine** (ACh) which targets two specific groups of receptors: muscarinic and nicotinic. Activation of the muscarinic receptors inhibits hypoglossal and can be blocked with atropine, a muscarinic antagonist. This likely occurs via presynaptic suppression of glutamate release. ACh also causes excitation through activation of nicotinic receptors that is masked by the overwhelming muscarinic effect [38].

In addition **GABA and glycine** are the primary inhibitory neurotransmitters acting at these areas. Glycine plays an essential role in REM sleep postural atonia. However, the actions of these neurotransmitters on hypoglossal muscles are still under debate [38]. In one study, strychnine, a glycine antagonist, completely abolished apneas and regulated ventilator effort in OSA [40].

Hypocretin (orexin-A) increases electromyographic activity in the genioglossus muscle and reductions in orexin in upper airway motor nuclei in NREM sleep could contribute to the suppression of upper airway dilator activity in NREM sleep [38].

In addition to the above, a number of lesser studied neuropeptides modulate brain stem motoneuron activity. Many of these have significant excitatory effects, e.g., **Vasopressin** binds to the V1A receptor on facial and hypoglossal motoneurons [41]. It may play a greater role in newborns as the receptor density declines with age [42].

There is binding of **Substance P** to the NK-1 receptor in the hypoglossal nucleus, and this declines with recurrent hypoxia [43]. Substance P (NK-1) agonists have been shown to be excitatory [44]. Hypoglossal motoneurons also possess **Oxytocin** binding sites [45], but their physiological significance is currently unknown. **Histamine** activity is also increased in the brain while awake and it is thus excitatory [38]. There may be more, as yet undiscovered substances that may have additional roles to play.

Hormonal Factors

Hormonal factors may also influence the activity of upper airway muscles. The genioglossal musculature in younger women is highly active compared to postmenopausal women and men of the same age. Thus, progesterone might be protective against sleep apnea. Exogenous progesterone administration has been shown to improve ventilation during sleep in men and women with sleep apnea [46]. Estrogen administration has been shown to decrease plasma levels of interleukin-6, which are higher in patients with sleep apnea [47]. Thus, postmenopausal women undergoing hormone replacement therapy (receiving progesterone and estrogen, both protective against OSA) have lower rates of OSA.

On the other hand, the exogenous administration of testosterone in women and healthy men can induce sleep apnea secondary to greater upper airway collapsibility independent of weight gain [48]. One cause might be greater deposition of soft tissue in the pharynx causing relaxation of the pharyngeal dilator muscles. This can because of redistribution of body fat under the influence of testosterone. This usually resolves if the exogenous testosterone is withdrawn.

Testosterone can also play a role in central apneas by altering the sensitivity of the central chemoreceptors to $PaCO_2$ [49].

Obese young females with polycystic ovary syndrome (POS) (who generally have higher circulating levels of androgens) develop sleep apnea at a higher rate than controls, and women with OSA have a higher level of circulating androgens hormones than do normal women paired by age and weight [48].

Thus, in relations to OSA, female hormones are protective and vice versa for male hormones.

Impact of Treatment

(a) Impact of treatment of OSA on depression and anxiety

CPAP treatment improves daytime sleepiness in patients with OSA. In clinical studies, improvement in daytime sleepiness often translates into improvement in the depressive and anxiety symptoms as most mood and anxiety scales have sleep-related questions.

The effect of CPAP on mood and anxiety is inconsistent. In a systematic review of 26 studies [50], nine evaluated the effects of CPAP on psychological status. Six of the studies used a comparison group for CPAP treatment other than pretreatment status. Three studies showed an overall improvement in psychological performance.

In the same review, eight studies looked at the effects of CPAP on depression. Five showed significant improvement, and none showed worsening. The authors concluded that CPAP has significant and positive impact not only on symptoms of sleepiness, but also on depressive symptoms.

In another review [51] the authors included studies in which patients were diagnosed with polysomnography for OSA and then subsequently treated for at least 3 months with CPAP. Various scales were used to evaluate for depression and anxiety. Four out of seven studies showed significant improvement in depression and anxiety.

Sanchez et al. [52] looked at randomized clinical trials in which CPAP was compared with more conservative measures like sham CPAP, oral appliances and placebos. In this review, five out of seven studies showed reduction in depressive scores with the use of CPAP. Comparison of CPAP with sham CPAP conducted by Yu et al. [53] showed significant reduction in mood scores (POMS (Profile of Mood States), except vigor subscale), which were not treatment specific, suggesting a placebo effect. Other authors reported significant lower depression scores (POMS and Hospital Anxiety and Depression Scale (HADS)) after CPAP treatment as compared with a control group [54, 55].

Published reports also show negative findings, suggesting that improvement of mood may not be clearly related to treatment of OSA. For example, Barnes et al. [56] compared CPAP with oral placebo and did not find significant difference between the two groups in quality of life and POMS and Beck Depression Inventory (BDI).

Engelman et al. [57] found no differences between CPAP and oral placebo on HAD scales.

There are discrepancies with regard to prevalence of anxiety and depression in patients with OSA. Although OSA is more common in men, various studies suggest that women have (or report more) depression than men [58].

Most authors suggest that treatment of OSA has an overall beneficial effect on quality of life and mood. The improvement in 'depression' may imply that CPAP is having an effect on epiphenomena such as fatigue, sleepiness and motivation rather than depression.

Impact of Treatment of Depression and Anxiety on OSA and CPAP Adherence

In some cases, treatment of comorbid insomnia and anxiety with a benzodiazepine and hypnotic may worsen OSA. These medications may decrease muscle tone in the already functionally impaired upper airway dilator muscles, blunt the arousal response to hypoxia and increase the arousal threshold for an apnea event, therefore increasing the number and duration of apneas [59].

Depression is known to have an effect on adherence to treatment of chronic medical conditions like cardiovascular disease, and treatment of depression tends to improve acceptance and compliance. Depressed patients might have poor adherence to CPAP use, suggesting that depression should be treated aggressively in these patients [60].

Patients with anxiety disorder, particularly with posttraumatic stress disorder (PTSD), have worse adherence to CPAP [61]. These patients complain of claustrophobia feelings with the use of CPAP. In some cases treatment of OSA improves subjective nightmares by reducing sleep fragmentation. Behavioral treatments like relaxation training and systematic desensitization can help some individuals get used to CPAP despite the feelings of claustrophobia [62].

Adherence to CPAP varies. In a pre/poststudy of 54 newly diagnosed OSA patients, neither pre-CPAP depression scores nor post-CPAP improvement in these scores were related to CPAP adherence [63].

In another study [64], depressive scores predicted poor CPAP adherence. Treatment of depression might improve acceptance of CPAP, reduce excessive sleepiness and improve quality of life, but this remains to be confirmed.

Central Sleep Apnea

Central sleep apnea (CSA) is characterized by cessation of airflow without respiratory effort. This is in contrast to obstructive sleep apnea, in which respiratory effort is present during breathing cessation.

In CSA, there are repetitive episodes of decreased ventilation due to complete or partial reduction in central neural outflow to the respiratory muscles. Congestive heart failure and dwelling at high altitudes are classical conditions in which CSA is present. Moreover, opiate pain medications also suppress breathing centers in the medulla and can cause CSA [65]. There are no studies looking at the relationship between CSA and psychiatric disorders or relationship of CSA caused by opiate pain medications and depression.

Hyperventilation syndrome is a behavioral condition in which minute ventilation exceeds metabolic demands, resulting in hemodynamic and chemical changes that produce dysphoric symptoms. Hyperventilation syndrome is frequently caused by anxiety and panic disorder. Behavioral hyperventilation, which is associated with anxiety, has been postulated to trigger CSA in three cases [66].

It is thought that patients who develop CSA have hypersensitive chemoreceptors, which respond briskly to increased CO_2 in the blood, resulting in overcompensating with hyperventilation and thus overshooting the apnea threshold [65]. In one study, authors found that children with congenital central hypoventilation, in which there is lack of chemoreceptor responsiveness to CO_2, have decreased anxiety rates. This might suggest that hypersensitive chemoreceptivity might be related to anxiety, though there are no studies available looking at this relationship [67]. With more attention to CSA and complex sleep apnea (central apneas triggered by CPAP therapy), we hope there will be studies looking at this possible complex relationship between anxiety, depression and central sleep apnea.

In the authors' clinical practice, most patients with CSA have insomnia and excessive daytime sleepiness, which could mimic symptoms of depression.

Effects of Sleep Loss on Mental Health

Sleep loss (referring, in general to less than 7–8 h per night) is highly prevalent and continues to worsen, as a result of both social factors (shift work, the availability of television, internet, etc.) and biological factors such as advancing age. The main symptom of sleep loss is excessive daytime sleepiness, but other symptoms include depressed mood and poor memory or concentration [68]. Chronic sleep loss can have serious consequences for health, performance and safety. It has been estimated that the percentage of men and women who sleep less than 6 h has increased significantly over the last 20 years [69]. Chronic sleep deprivation and sleep disruption affect a wide range of body systems.

Neuroendocrine and Hormonal Effects

Sleep disruption is a stressor and, like all stresses, activates the body's established stress–response systems: the autonomic sympathoadrenal system and the hypothalamic–pituitary–adrenal (HPA) axis system [70]. This causes significant disruption of cortisol and adrenocorticotrophic hormone (ACTH) levels. Numerous studies have reported a higher prevalence of obesity, impaired glucose tolerance and diabetes in subjects with partial or total sleep deprivation after controlling for age, Body Mass Index (BMI) and other confounders [71].

Changes in the serum levels of both growth hormone [72] and prolactin [73] have also been documented in patients with OSA. Thyroid activity, including TSH, T3 and T4 levels is increased by sleep deprivation [74]. In general, sleep appears to suppress stress systems and results in lower plasma levels of stress hormones such as cortisol and adrenaline.

Behavioral/Cognitive/Mental Health Effects

Excessive sleepiness, fatigue, irritability and decrease in concentration have been documented as the effects of sleep deprivation. In addition longer reaction times, poor short-term memory, reduced motivation, distractibility and poor performance are also associated with both sleep deprivation and sleep fragmentation [75].

Even if the total sleep time remains the same, fragmentation of sleep (such as occurs in OSA) has been shown to impair functioning including reduced vigilance and reaction times [75]. OSA causes chronic sleep deprivation as well as changes in normal sleep architecture. This results in numerous cognitive problems including deterioration in memory, intellectual capacity and motor coordination as well as a decline in psychomotor vigilance. In addition, it can result in personality changes, irritability, depressive symptoms and an increased proneness to accidents [76].

The relationship between sleep disorders and psychiatric illness is bidirectional. Psychiatric disorders and their treatment can cause or contribute to sleep problems, and psychiatric illness can also be a consequence of sleep disorders [14]. Effective treatment for OSA has been shown to improve mood symptoms [32].

Conclusion

Clinicians must consider depression and anxiety disorders as comorbid conditions in every patient with OSA. Patients with depression and anxiety might present with sleep-related complaints such as insomnia, fragmented sleep, or daytime sleepiness. The sedative effects of psychotropic medications can often mimic the residual symptoms of daytime sleepiness in patients with OSA.

As OSA is associated with a higher prevalence of psychiatric comorbidities, patients with residual symptoms of daytime sleepiness and fragmented sleep should be screened for depression and anxiety so they could be appropriately referred for treatment of their psychiatric condition.

CPAP adherence is poor in patients with depressive and anxiety disorders. Attention to barriers to the use of CPAP is important in these patients as it might improve adherence.

Psychiatric illness exists in close conjunction with sleep disorders. Comorbid mental illness and sleep disorders increase disease burden and produce adverse long-term outcomes. Patients with sleep disorders need to be screened carefully for psychiatric illness and, where necessary, concomitantly treated for comorbid psychiatric illness.

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Chapter 9
The Impact of Comorbidities in Patients with Chronic Respiratory Diseases

Abebaw Mengistu Yohannes, PhD, MSc

Introduction

Chronic respiratory diseases primarily affect the lung. Asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, lung cancer, lung fibrosis, sleep apnoea syndrome, pneumoconiosis and pleural diseases are common respiratory diseases worldwide [1]. They present similar symptoms such as breathlessness on exertion, excess mucous production, chronic cough and wheezing. When these conditions are not adequately treated and/or become chronic may contribute to the development of systemic inflammatory comorbid disorders such as cardiovascular, musculoskeletal, psychiatric and cerebrovascular diseases. These comorbid disorders and pathophysiological mechanisms may vary in their manifestations, despite having similar symptoms. Thus, it is beyond the scope of this chapter to cover all chronic respiratory diseases with their comorbid disorders to explain in detail. COPD was chosen because it is the most common respiratory disease, as an example, to explain and illustrate the impact of the resultant comorbidities and their management. In addition, the chapter briefly comments about comorbidities in Asthma and where appropriate references were made to other chronic respiratory diseases.

COPD is a major cause of morbidity and mortality in old age. In 2004, WHO [2] estimates about 210 million people are living with COPD worldwide. Out of these, 65 million have been physician diagnosed with moderate-to-severe COPD. It is quiet staggering number; only less than one third of the patients have been diagnosed with the disease. The majority of the people are living unaware of such a progressive disabling (debilitating) disease, which may have a major impact on their daily physical functioning, social interaction and their quality of life.

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The rationale behind why a large proportion of patients with respiratory impairment remain undiagnosed with the disease is unclear. It is most likely to be a multifactorial including (e.g. lack of spirometer in practice to make accurate diagnosis), lack of public perception awareness the impact of respiratory disease(s), lack of dedicated service and staff manpower to manage patients with respiratory problems especially in developing countries and inadequate funding availability for chronic respiratory diseases research [3] compared with other chronic diseases for example, cardiovascular disease. Furthermore, in terms of disease and societal burden, COPD is projected to be the third leading cause of mortality by 2030 [4]. For example, in the USA, despite medical advancement in producing effective drug therapy for clinical management of COPD, in the past three decades, the death rates from COPD has been exponentially rising almost by twofold, while a significant decline observed in death rates from heart disease and stroke in the same period [5].

The recent Canadian population-based study from the administrative data (approximately 13 million people) [6] investigated the lifetime risk of developing of COPD. They found that the incidence of COPD was rising with increasing age. Men are at a higher lifetime risk of developing COPD compared to women. Those who live in rural areas and lower socio-economic status are at elevated risk of developing COPD compared to their counterparts of urban community-dwellers and higher socio-economic status, respectively. The lifetime incidence rate of physician-diagnosed COPD at the age of 50 was 2.6% (1000 person-years by age) and at the age of 80 years was 27.6% [6]. The exponential rise in the incidence of COPD with increasing age is quiet alarming and challenging. It is possible that older people are less likely to appreciate the subjective reduction in the perception of bronco-constriction and low expectation in physical functioning because of their age [7].

A population-based study in Italy (over 7 million people) [8] showed that the prevalence of COPD in adults aged 45 years and older was 3.6%. Of these, 126,283 COPD patients, the prevalence of COPD was related with increasing age. The prevalence of COPD was 1.9% in the age group 45–64 years, 4.8% in 65–74 years, 6.8% in 75–84 years and 5.6% in over 85 years. There was a significant gender difference in the prevalence of COPD, more common in males compared to women (4.1% in males and 3.1 in females). Historically and epidemiological evidences showed that men were high tobacco consumers (taking into account average pack-years) compared to women. This partly may have contributed to a high prevalence of COPD and deaths rate in men. In contrast to this, the recent mortality data, from the USA indicated that the number of women dying from COPD was surpassing that of men dying from COPD [9]. Why this might be a disease that requires further exploration? In 2012, Perera et al. [10] published a study that examined in the US the national inpatient survey of burden of acute exacerbations of COPD and the impact of comorbidities on inpatient costs and mortality. Their findings showed that women had more comorbidities compared to men. The total costs of managing COPD patients (n = 1,254,703 hospitalization) with acute exacerbations was US$11.9 billion. The inpatient mortality during admission was 4.3% (n = 53,748). A number of comorbidities (acute myocardial infarction;

congestive heart failure; cerebrovascular disease; lung cancer; cardiac arrhythmias; pulmonary circulation disorders; and weight loss) may have contributed for both inpatient mortality and for incremental costs. In light of these findings, this chapter intends to update and synthesize the impact of comorbidities especially cardiovascular disease, depression and anxiety and lung cancer in patients with COPD. It will also explore the impact of other comorbidities on quality of life and healthcare utilization. Finally, it will provide succinct summary of clinical tips in how to manage these comorbid disorders.

Comorbidity implies to a disease coexisting with the main diagnosis of the patient, for example, the occurrence of depressive symptoms after the initial diagnosis of COPD. Comorbidities contribute to a substantial burden in increased disability and mortality in COPD patients in old age [5, 8, 9]. The causes of comorbidities in COPD patients are multifactorial and their manifestations are less clearly understood. There are several potential mechanisms for COPD patients to develop comorbidities compared with the general healthy population. COPD primarily affects the lung, and the irreversible and progressive nature of respiratory impairment and chronic inflammation of the disease are often associated with systemic manifestations outside the lung. The ongoing chronic inflammation of the airways in the lung especially those continued smoking with COPD and alterations in repair and in immune mechanisms tends to affect other organs and cardiovascular system in the body. Barnes and Celli [11] describe this phenomenon as the 'spillover' of the local airway inflammation through 'inflammatory mediators into circulation may result to develop systemic manifestations of the disease, e.g. skeletal muscle wasting and cachexia'. Systemic inflammation (interleukin-6, interleukin-B and tumour necrosis factor) in turn may lead to worsen health status of patients with comorbid diseases, e.g. cardiovascular diseases.

A recent meta-analysis by Gan et al. [12] identified that reduced lung function was associated with raised levels of systematic inflammatory markers such as C-reactive protein (CRP), fibrinogen, leucocytes and tumour necrosis factor-alpha (TNF-alpha) in COPD patients compared with healthy controls. In addition, others have demonstrated [13] that lung function decline and systemic inflammation exhibited by the presence of elevated fibrinogen levels may contribute to frequent acute exacerbations in patients with COPD. Thus, further work is needed to explore the role of inflammatory markers in the pathogenesis of acute exacerbations in order to improve the clinical management of patients with COPD.

Comorbidities from Population-Based Studies

A recent Danish Nationwide population study of 7.4 million people [14] examined the prevalence of COPD and related comorbidities. Out of these, 313,958 people were suffering with COPD. The five common comorbidities in COPD patients were: 57,129 (18%) myocardial infarction, 32,577 (10.3%) diabetes, 24,408 (3.5%) lung cancer, 11,172 (3.5%) depression and 9608 (3%) with hip fracture. In addition,

findings from the epidemiological cross-sectional study in Italy [7] revealed that the three common comorbidities with high prevalence were cardiovascular disease 80,840 (64%), diabetes 17,091 (12.4%) and depression 10,292 (8%). Furthermore in 2009, a nationwide telephone survey in the USA, in randomly selected of (n = 1003) COPD patients [15] the most commonly reported comorbidities were hypertension (58%), hypercholestromeia (52%), depression (37%), cataracts (31%) and osteoporosis (28%). Furthermore, a recent US retrospective observational study of 183,681 patients with COPD from a large administrative claims data set [16] identified that the four common comorbidities were cardiovascular disease (34.8%), diabetes (22.8%), asthma (14.7%) and anaemia (14.2%). Over 52% of the COPD patients had one or more comorbidities that significantly affect their daily activities and quality of life.

The variation in the spectrum of phenotype of comorbidities in patients diagnosed with COPD, population surveys are most likely because of heterogeneity of the sample, and the various methodologies adopted to collect data in different countries. The impact of comorbidities in COPD patients are multidimensional including increased risk of high levels of anxiety, decreased in physical functioning due to disuse muscle weaknesses and reduced in social interaction and dependency on caregivers in daily activities. All these factors may contribute to significant impairment in COPD patients' physical activities and their quality of life as 'disease burden' increases illustrated in Table 9.1. Therefore, there is great uncertainty and

Table 9.1 Comorbidities in patients with COPD

Cardiovascular diseases
• Hypertension
• Myocardial infarction
• hypercholestromeia
• Congestive heart failure
• Stroke
Metabolic syndrome
• Diabetes
• Vitamin D deficiency
• Anaemia
• Obesity
Psychological and physical problems
• Depression
• Anxiety
• Fatigue
Musculoskeletal problems
• Osteoporosis
• Hip fracture
• Sarcopenia
Terminal disease (life-limiting) disease
• Lung cancer
Others
• Obstructive sleep apnoea
• Chronic Asthma
• Cataracts
• Erectile dysfunction

challenges for the healthcare professionals in how best to treat elderly COPD patients with multiple comorbid chronic diseases including the potential drug side effects and toxicity.

Asthma and Comorbidities

Asthma is a common airway inflammatory disorder characterized by variable airway obstruction and hyperresponsiveness. It affects over 300 million people worldwide [1]. Uncontrolled asthma is a major cause of hospital admission and increased psychological morbidity in all ages. Boulet and Boulay [17] in a recent review identified that the most common comorbidities in patients with Asthma include rhinitis, sinusitis, gastroesophageal reflux disease, obesity, obstructive sleep apnoea, hormonal disorders and psychopathologies. These respiratory disorders share similar pathophysiological mechanism with asthma may influence asthma control, its phenotype and treatment.

Chronic asthma may coexist or develop to COPD especially in smoking asthmatic patients. Studies have shown that asthmatic patients who smoke may have early COPD, as indicated by more severe airway obstruction and lower carbon monoxide diffusion capacity [17, 18]. A recent systematic review [18] reported about 15–20% of COPD patients may have the asthma-COPD overlap syndrome (ACOS). ACOS is defined as with symptoms increased variability of airflow in association with an incompletely reversible airflow obstruction. Furthermore, patients with ACOS have more frequent exacerbations, more wheezing and dyspnoea, but similar cough and sputum production compared with COPD [18].

Recent clinical guidelines advocate [19] the identification and treatment of comorbidities should be an integral part of the chronic asthma management. Therefore, a comprehensive disease-management approach that is individually tailored which include education, weight loss management (diet and exercise), cognitive behavioural therapy and smoking cessation program are worthy of consideration for asthmatic patients with comorbid disorders.

Healthcare Utilization and COPD

In 2007, in the USA, the overall cost of COPD, pneumonia and asthma was approximately $85 billion. Out of these, $66 billion was for in direct healthcare expenditures (hospital and professional services, medication, medical equipment), and $19 billion was for in indirect mortality costs [20]. Of these expenditures, the large proportion of the healthcare budget was spent on patients with COPD. In 2002, Mannino et al. [9] reported that COPD was responsible for 8 million physician office and hospital outpatient visits, 1.5 million emergency department visits, 726,000 hospitalizations and 119,000 deaths. In five-year surveillance population-based

study in Denmark, Blide et al. [21] examined the healthcare utilization in patients with COPD compared with the general population. The findings showed that COPD patients were (12 times per year) more likely to consult general practitioners for their health problems than patients without COPD. The total cost of managing COPD was over 256 million euro (approximately US$332 million). Further detailed analysis revealed that only one third of the cost was accounted for the primary diagnosis of COPD. Two-thirds of the COPD-related costs were mainly due to admissions for other diseases such as comorbid cardiovascular diseases, other respiratory diseases (e.g. pneumonia) and cancer. Thus, signify COPD patients with comorbid diseases are most likely to be high healthcare users compared without comorbidities. In a separate study [22] in the USA, COPD patients were more likely to utilize healthcare services and had excess total healthcare costs about $20,500 higher ($p < 0.0001$) than the comparison cohort of non-COPD patients. Comorbidities in COPD patients were high, accounting for 46% of the observed excess cost. Of these, 'the impact on total healthcare costs was greatest for anaemia ($10,762 more, on average, than a patient with COPD without anaemia)' [16].

Undiagnosed and/or in-adequately treated comorbidities in COPD patients will have detrimental effect on patients' health status and substantial care burden to caregivers. COPD patients with several comorbidities are most likely to consult their general practitioners more frequently compared with one or two comorbidities [14, 19, 21]. COPD patients with multiple comorbidities are most likely to experience frequent episodes of acute exacerbations, with longer days of hospitalization and use more intensive care or high-dependency units compared without comorbidities [19, 20].

Cardiovascular Diseases in COPD

Cardiovascular diseases (CVD) and COPD are projected to be the second and fifths leading causes of mortality worldwide by 2030 [23]. In addition, COPD patients with comorbid CVD are most likely to live with increased burden of physical disability and impaired quality of life. The direct and indirect economic costs to the healthcare providers and the society are most likely to be enormous. In 2008, a retrospective cohort study in the USA by Dalal et al. [24] examined the total healthcare costs of COPD patients with CVD aged ≥ 40 years from the administrative data ($n = 6000$). They showed that the annual average direct medical costs per patient for COPD patients with comorbid CVD was $22,775 compared without CVD was $8036 ($p < 0.001$) and total costs were $27,032 versus $11,506 ($p < 0.001$), respectively. Furthermore, COPD patients with comorbid CVD twice most likely to be hospitalized and 47% more likely to have emergency room visits in a previous year compared with COPD patients alone. This provides some evidence that the healthcare professionals should treat CVD aggressively in order to reduce the burden in COPD patients, improve their quality of life and reduce healthcare cost.

Association of CVD with Systemic Inflammation and Vascular Damage

Both CVD and COPD share similar risk factors for developing the disease such as cigarette smoking and environmental air pollutions. However, the mechanism by which COPD patients develop CVD is unclear. Atherosclerosis is the main cause of CVD. Therefore, the early detection of atherosclerosis is crucial to identify patients with high risk in developing CVD and in planning appropriate intervention. Vascular function can be assessed non-invasively by measuring endothelial function and arterial stiffness, using pulse wave analysis derived measures (pulse wave velocity and augmentation index).

A recent study by MacLay et al. [25] with a relative small sample size (n = 18 COPD patients, n = 17 healthy controls) examined the vascular dysfunction of the participants with a lifetime exposure of smoking, controlling for the cardiovascular risk factors. They found that COPD patients have greater stiffness mean (SD) [pulse wave velocity, 11 (2) vs. 9 (2) m/s; p = 0.003; augmentation index, 27 (10) vs. 21 (6)%; p = 0.02] compared with health controls, independent of cigarette smoking exposure. In a larger prospective study (n = 102 COPD and n = 103 healthy controls), Mills and et al. [26] examined whether the occurrence of arterial stiffness and blood pressure in patients with COPD was higher than with age in a smoking matched healthy controls. Increased arterial stiffness and high blood pressure were exhibited in COPD patients compared with the healthy controls. In addition, serum C-reactive protein concentrations were threefold higher in COPD patients compared with healthy controls mean (SD), (6.1 (0.9) vs. 2.3 (0.4) mg/l; p = 0.001). Systemic inflammation and vascular dysfunction are the potential risk factors through which for COPD patients to develop cardiovascular disease. However, the exact mechanistic link is unclear, because of the study designs and relative small sample size to determine the causal association between COPD and vascular dysfunction. Larger randomised control trials are required.

Curkendall et al. [27] in a three-year follow-up study (n = 11,493) examined the incidence of cardiovascular events in patients with COPD. Their findings indicate that COPD patients with CVD experienced threefold to fourfold of increase in the rate of fatal cardiovascular events compared without COPD. In addition, COPD patients with comorbid CVD had twice the risk of premature mortality 2.07 (CI: 1.82–2.36) and all cause of mortality 2.82 (CI: 2.61–3.05) in comparison without CVD. In a separate study by Sidney et al., in a longitudinal study, [28] examined the relationship between COPD, incidence of CVD, hospitalization and mortality of patients with COPD (n = 45,966), with a similar number of the control group in four-year follow-up. They found that COPD was a risk factor for elevated cardiovascular-related mortality and hospitalization. Younger COPD patients (aged < 65 years) and female patients were at high risk of developing CVD. Therefore, CVD risk should be monitored and treated with particular care in

younger adults with COPD. Hackett et al. [29] examined between the gene environment interactions, smoking and inflammatory markers (IL-6, interferon-y, interleukin-1b,) and COPD. Findings from this study showed that a polymorphism in the gene encoding IL-6 interacts with smoking history to influence the rate of lung function decline in patients with COPD as well as their risk of cardiovascular disease. A recent systematic review by Clarenbach et al. [30] postulated that systematic inflammation, oxidative stress, hypoxia, sympathetic activation and physical inactivity might be potential mechanisms in COPD leading to vascular dysfunction and cardiovascular disease as Shown in Fig. 9.1.

Periodical evaluation of these clinical markers may play an important role to improve prognosis and reduce premature mortality in this patient group.

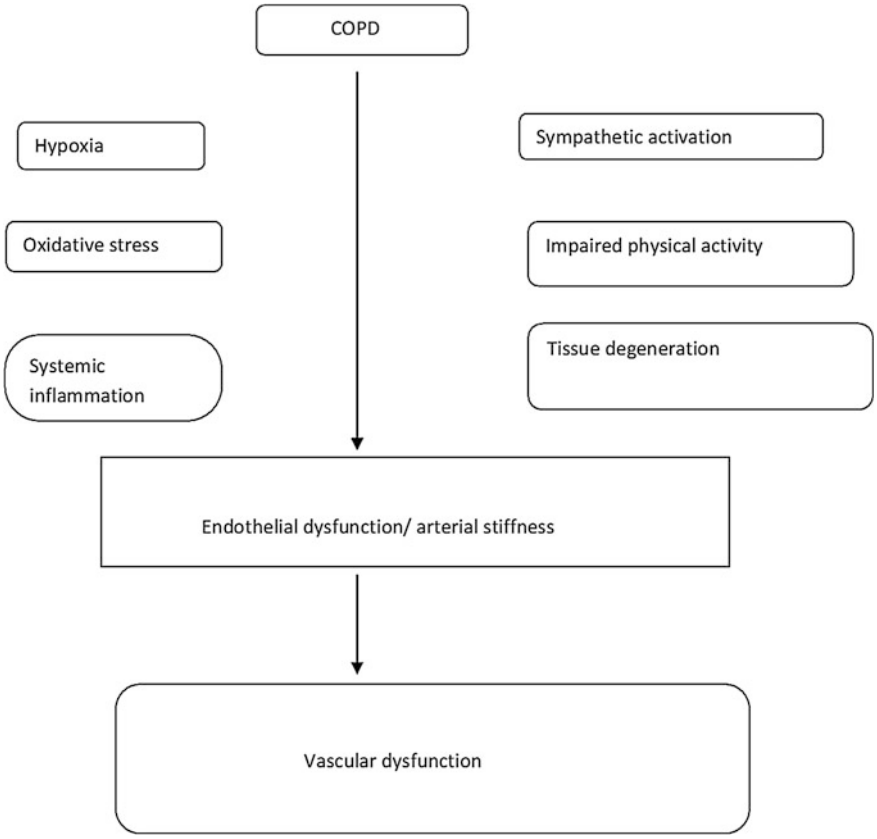

Fig. 9.1 Postulated mechanisms of vascular damage in chronic obstructive pulmonary disease. From Clarenbach et al. [30], with permission of Taylor & Francis Ltd, www.tandfonline.com

Myocardial Infarction

A recent UK primary care-based survey [31] by Schneider and colleagues investigated the prevalence of comorbidities in COPD patients (n = 35,700) identified that patients with COPD have a higher risk of developing myocardial infarction (40%), cardiac arrhythmia (19%), stroke (13%) and deep vein thrombosis (35%) compared with COPD-free counterparts. In a similar setting, Feary et al. [32] examined factors that are associated with COPD from computerized database primary care records of 1,204,100 million people in the UK. Physician-diagnosed COPD was associated with increased risks of CVD (odds ration 4.98, 95% CI 4.85–5.81; $p < 0.001$), stroke (odds ratio 3.34, 95% CI 3.21–3.48; $p < 0.001$) and diabetes mellitus (odds ration 2.04, 95% CI 1.97–2.12; $p < 0.001$). Further analysis was performed adjusting for the confounding factors sex and smoking status and stratifying for age. Their findings indicate that the greatest increase in the rate of 'acute arteriovascular events was found in the youngest age groups, the hazard ratio for acute MI was 10.34 (95% CI 3.28–32.60; $p < 0.001$) and for stroke the hazard ratio was 3.44 (95% CI 0.85–13.84; $p < 0.001$) compared with the oldest age group'. They have highlighted the importance of an integrated collaborative treatment approach to deal with the excess comorbidities. McAllister et al. [33] in a prospective study (n = 242) COPD patients aged 40 years and above admitted with acute exacerbations with a smoking history of 10 pack-years were examined at discharge to determine the potential risk factors to develop MI. Their findings showed that 1 in 12 of patients met the diagnosis criteria for MI. None of the patients was receiving appropriate care for comorbid MI. This indicates undiagnosed MI was relatively common in patients with COPD. Future research has to focus on early detection and treatment strategies to reduce the risk of MI in COPD patients.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is common in patients with severe advanced COPD, but the prevalence in mild-to-moderate COPD is unknown. Thabut et al. [34] explored the prevalence of PAH in severe COPD patients (n = 251) who had a lung volume reduction surgery or lung transplantation surgery. Over fifty per cent of the COPD patients were identified with hypertension with mean pulmonary artery pressure (PAPm) > 25 mm Hg, but in patients with moderate (PAPm, 35–45 mm Hg) or severe (PAPm > 45 mm Hg) in 9.8% and in 3.7% of COPD patients, respectively. The severity of pulmonary hypertension was associated with the severity of lung function impairment and with hypoxia. The exact mechanism in how pulmonary hypertension manifest in COPD patients is unclear. It is most likely to be multifactorial. Variables that increase pulmonary vascular resistance may also increase the 'pulmonary wedge pressure of left ventricular dysfunction or severe

airway obstruction with wide intrathroacic pressure swings, and destruction of lung parenchyma leading to loss of part of the pulmonary vascular bed may play a role' [35]. Given this proposition in patients with mild-to-moderate COPD, the pulmonary arteries may exhibit an enlarged intima, because of the proliferation of poorly differentiated smooth muscle cells and deposition of elastic and collagen fibres, with reduction in the lumen and arteriolar muscularization [36]. However, the contribution of hypoxic vasoconstriction to the ventilation-perfusion ratio balances to be greater in mild COPD but is less active in moderate-to-severe COPD. All these changes may contribute to the dysfunction of the vascular structure and function in COPD patients, for detailed review see [35]. The exact role of systemic inflammation in PAH patients is unknown. Peinado et al. [36] have shown that (current cigarette smoking was associated with elevated CD8+ T-lymphocytes and neutrophils) inflammatory process in the pathogenesis of pulmonary vascular abnormalities in the early stage of COPD. Furthermore, vascular abnormalities impair gas exchange and may result in pulmonary hypertension, which is one of the principal factors associated with reduced survival in COPD patients [35, 36].

The management of COPD patients with PAH requires a systematic and coherent treatment approach. Minai et al. provide [35] the most helpful strategy in the management of PAH in COPD patients: (1) confirm the diagnosis using Doppler echocardiography; (2) optimize COPD management; (3) rule out other comorbidities; (4) assess and treat hypoxemia; and (5) enrol the patient to pulmonary rehabilitation programme.

Table 9.2 provides variable related to develop cardiovascular diseases the majority are modifiable risk factors, which fall under the umbrella lifestyle issues. Thus, coordinated, integrated and innovative public healthcare programme is most likely to be beneficial for patients with COPD. Therefore, the focus should be to change attitudes and maximize lifestyle-related interventions for self-management. Those COPD patients with high-risk CVD profiles should be referred to experts in the field for proper assessment and treatment and periodically monitored by their general practitioners. It is advisable for patients to be encouraged in a self-management programme to stop cigarette smoking, to be involved in a regular physical exercise programme, e.g. regular walking exercise 2–3 times per week for the duration of 30 min. It is beyond the scope of this chapter to discuss the whole

Table 9.2 Risk factors associated with cardiovascular diseases

Cigarette smoking
Hypertension
Obesity
Physical inactivity
Unbalanced diet
High salt intake
Systemic inflammation
Vascular dysfunction
High blood pressure
Excessive alcohol consumption
High cholesterol

medical management for patients with cardiovascular diseases. Therefore, readers are encouraged to read the detail guidance provided by the WHO and the National Institute for Clinical Excellence guidelines for cardiovascular diseases [37, 38].

Depression in COPD

Depression is common in patients with COPD. A recent systematic review in our department [39] identified the prevalence clinically significant depression was between 8 and 80%. This is comparable to patients with chronic heart failure with clinically importance of depression range between 10 and 60%. The recent update of the National Institute Clinical Excellence for the management of COPD highlighted the importance of early screening and treating depression effectively to remission [40]. Untreated and under-recognized depressive symptoms in patients with COPD were associated with poor adherence with medical treatment [41], early dropout from pulmonary rehabilitation [42], frequent consultations with the general practitioners and frequent episodes of emergency care and hospital admission, and all these factors may contribute to premature mortality [39–41].

Risk Factors Associated with Depression in COPD

There are a number of risk factors that are associated with elevated depression in patients with COPD including increase in physical disability, low socio-economic status, social isolation, reduced lung function and low body mass index [39, 40]. In addition, an increase in physical disability was a predictive factor for the subsequent onset of depression in the preceding year. Depression in COPD patients often interferes with self-care management, adherence to medical treatment, persistence in active smoking and loss of interest in pleasurable activities, in turn all these factors may lead to a gradual decline in health status and social interaction [39–42]. However, there is limited understanding in terms of the pathways to trigger depression in patients with COPD. The interaction between COPD and developing depressive symptoms in older patients is dynamic in nature, but the exact mechanism it manifests is not fully understood. It is likely to be a multifactorial.

The pathway in which COPD patients develop depression is not clear. It is most likely as the result of complex interaction between physiological, physical and psychosocial factors. There is a possibility of a bidirectional two-way relationship. Smoking cigarette is the main cause of developing COPD. It is possible that COPD patients with depression are most likely to continue smoking because of loss of interest or motivation to quit due to the low mood. Therefore, there is a link between smoking cigarettes and depression but the particular mechanism is not clear. It does not follow a single pathway. Future studies may explore the bidirectional relationship in a longitudinal study, and the aetiology of

depression in elderly patients with COPD, e.g. the relationship with cardiovascular diseases and degenerative changes in the brain.

Minor depressive symptoms that do not meet the criteria for major depression are common in patients with COPD [43] and point of prevalence estimated at 25%. They are associated with increased physical disability and impaired quality of life in patients with COPD and part of continuum with major depression [44, 45]. Depression has been associated with increased healthcare utilization [45], episodes for frequent hospital readmission and longer days of hospital stay [46] and premature mortality [47]. Katz et al. [48] in a longitudinal study identified increased physical disability was a strong predictive factor for the new onset of depression.

A recent review [49] showed that pulmonary rehabilitation in a short term may be useful in reducing anxiety and depressive symptoms in patients with COPD. However, the long-term efficacy is unknown. A few studies [50, 51] have shown that cognitive behavioural therapy (CBT) helps to reduce depressive symptoms in patients with COPD. It is quiet promising and novel treatment approach to incorporate CBT as part of routine clinical practice. Currently, CBT is quiet scarce for the wider healthcare provision. Innovative approach such as web-based CBT is worthy of consideration.

The use of antidepressant drug therapy for COPD patients with depression is inconclusive [52]. It is partly to do patients refusals to receive antidepressant drug therapy. It is possible that patients do not see the relevance of treatment seeing the gloomy picture of their condition or the impact of depression in their life. Some of the perceived barriers reported by the COPD patients include: Stigma attached to depression, afraid of side effects, Fed up, angry, denial and not bothered, fear of being addicted to antidepressant medication, belief that having depression is a weakness and frustrated with taking too many drugs [43, 52].

Therefore, it is important to teach and educate patients about the perceived barriers of treatment of depression in COPD patients. The collaborative care model using a case manager has been shown to be beneficial to improve treatment adherence and improve depression treatment [53]. Therefore, further work is required to determine the cost efficacy of this kind of treatment approach.

Anxiety

The prevalence of potentially clinical anxiety symptoms ranges between 6 and 74% in patients with COPD [39]. This figure is similar to patients with chronic heart failure with anxiety symptoms, which was between 11 and 45%. Anxiety has been shown to be associated with poor health outcomes including decreased in exercise tolerance, with greater risk of self-related functional limitations, frequent episodes of hospital readmission and impaired quality of life [54, 55].

Anxiety disorders in patients with COPD are heterogeneous than depression, including diverse diagnoses such as generalized anxiety disorder, social phobia, phobic anxiety, obsessive-compulsive disorder and post-traumatic disorder [56].

There is very little or no epidemiological data available to determine the accurate prevalence of these disorders in patients with COPD. In addition, the management of anxiety in patients with COPD is often suboptimal. Kim et al. [57] reported that only a quarter of people with COPD and moderate-severe anxiety were receiving appropriate treatment. Two studies have shown that CBT was effective in reducing anxiety symptoms in patients with COPD [50, 51]. Kunik et al. [50] demonstrated that there was no difference in the efficacy between educational programme and CBT in 12-month follow-up programme in reducing anxiety symptoms in patients with COPD. Therefore, larger randomized controlled trials are needed to examine the cost efficacy of CBT in patients with COPD.

Lung Cancer in COPD

Lung cancer is an overwhelming additional life-limiting disease with profound impact on COPD patients' survival, impairing their quality of life, compromising their coping strategies and increases caregivers' anxiety and burden.

The prevalence of lung cancer in patients with COPD estimated between 40 and 70% dependent on diagnostic criteria, age, gender and duration of smoking exposure [58, 59]. Wasswa-Kintu et al. have shown that COPD patients are four times likely at a risk of developing lung cancer [60] compared with smokers with normal lung function. After controlling for the disease severity, a recent meta-analysis reported that an established diagnosis of COPD plus radiologic evidence of emphysema gave 2.64 times relative risk of lung cancer compared with non-COPD patients [61]. Furthermore, Young et al. [59] have demonstrated the prevalence of COPD in newly diagnosed lung cancer cases was sixfold greater than in matched smokers. In a separate study by de Tores et al. [62], the incidence of lung cancer in patients with COPD was (incidence density of 16.7 cases per 1000 person-years) higher compared to 4.2 cases per 1000 person-years in Towards a Revolution in COPD Health [63]. In this study, the most frequent type of histological subtype was squamous cell cancer (44%). Others have reported [62] that COPD increases the risk of the squamous cell histological subtype by more than four times, while chronic bronchitis relates to adenocarcinoma.

The risk factors to develop lung cancer are multifactorial. A recent editorial [64] from our department reported that COPD patients with the following characteristics are prone (susceptible) to develop lung cancer:

- Older people with COPD
- Low body mass index
- Active smoking status
- Diffusion capacity for carbon monoxide <80% predicted
- Global Initiative for chronic obstructive lung disease stages (I and II)
- Severe COPD
- Emphysema

- Chronic airway inflammation
- Inhaled corticosteroids
- Occupational exposure to diesel motor exhaust
- Occupational exposure to organic dust.

The disease manifestations are multifactorial. The pathological processes are incompletely understood. It is most likely as the result of complex interaction of physiological (lung function impairment), environmental pollutions (fumes and dusts), social habits (active smoking) and chronic inflammation, which predispose COPD patients to lung cancer [63, 64]. In addition, the potential mechanisms for the increased risk lung cancer in COPD are unclear. Chronic inflammation, which is common in COPD, is most likely to play an important role in the pathogenesis of lung cancer. Given this proposition, patients with COPD are most likely to experience a multiple episodes of respiratory infection with two or three times the rate of hospital admission per annum [40]. Papi et al. [65] have postulated that repeated chest infections tend to affect the function of the mucociliary clearance system, compromising its ability to remove carcinogens and other damaging substances present in cigarette smoke. This may contribute for the development of airways obstruction in the distal airways that may lead to emphysema. Furthermore, persistent exposure of the bronchial epithelium to active cigarette smoking precipitates irritation of the lumen, which allows carcinogens for increased access to the epithelium (increase permeability) and produces low-grade inflammation over a period of time and these carcinogens may promote pathologic changes leading to squamous cell neoplasia [65].

In 2011, a comprehensive review by Raviv et al. [66] examined the surgical options for patients with COPD with comorbid lung cancer. The review showed that surgical intervention (e.g. tumour resection, lobectomy and combining lung volume reduction surgery) with curative intent may have better survival outcomes compared with non-surgical intervention. However, COPD patients with lung cancer often do not fulfil the inclusion criteria for surgery because of the severity of lung function impairment and poor exercise tolerance. Therefore, further work is required to determine the efficacy of various options of surgical procedures in randomized controlled clinical trials. Current availability of palliative care for patients with severe COPD is very scant. Those COPD patients identified with lung cancer should receive a holistic and integrated palliative care treatment to improve their quality of life and reduce healthcare cost.

Osteoporosis in COPD

Osteoporosis is one of the systemic features of COPD. It is a systemic skeletal disease characterized by low bone mineral density (BMD) and micro architectural changes in bone tissue that increases the susceptibility to fractures [67].

Anaemia in COPD

A recent systematic review [68] identified the prevalence of comorbid anaemia in patients with COPD ranges from 7.5 to 34% depending upon the populations selected and diagnostic tools employed to determine the level of haemoglobin. Comorbid anaemia in patients with COPD was associated with greater healthcare resource utilization, impaired quality of life, older age and male gender. Furthermore, anaemia in patients with COPD is an independent prognostic predictor of premature mortality and a greater likelihood of hospitalization.

Although the precise cause of anaemia in COPD patients is unknown, there appears to be a relationship with certain proinflammatory markers suggesting that at least a component of the observed anaemia in that often attribute to inflammation i.e. the anaemia of chronic inflammation) [69]. Moreover, the cause of anaemia in patients with COPD is most likely that observed in other chronic inflammatory diseases including nutritional deficits, stress ulcer (especially those on steroids) carboxyhemoglobin effects of cigarette smoking. Compromised oxygen delivery may also impact cardiac and renal function [68].

To date very little work has been done to treat comorbid anaemia in randomized control trial setting in patients with COPD. Therefore, robust and prospective studies are needed in well-characterized COPD patients to determine the true prevalence, consequence of concomitant anaemia and efficacy of intervention. Furthermore, research design should include longitudinal assessment to both lung function and haemoglobin level to account for any changes during exacerbation-free periods in patients with COPD and to establish the influence of anaemia on the natural history of COPD.

Cognitive Impairment

Cognitive impairments such as problems with working memory, executive functioning, visuospatial and attention are common in patients with COPD. Untreated cognitive impairments may compromise an individual's ability to manage his/her own personal care, dependency on caregivers, non-adherence to medical treatment or rehabilitation, increase disability and healthcare utilization [70]. The latest systematic review and meta-regression analysis in our department [71] in patients with COPD showed one in four patients had MCI. None of the studies reported the efficacy of intervention to treat MCI. Future work should focus on ways of detection, managing and treatment of MCI in this patient group.

Clinical Implications of Comorbidities

Comorbid conditions may influence the diagnosis and assessment of the severity, self-management and control of patients with chronic respiratory diseases.

Evidence from the available literature suggest that the effect of treating comorbidities in patients with chronic respiratory diseases and long-term clinical outcomes are uncertain. Thus, well-controlled randomized control trials are needed.

All the projections indicate that COPD and asthma are growing problems worldwide and the incidence are most likely to rise in the next few decades before they level off. They may warrant public awareness campaign of their burden and screening healthy populations' especially current smokers for early detection and treatment of COPD and asthma.

Comorbidities are common in COPD and asthma patients. Current medical approach is not sufficient to alleviate social and economic burden of the disease. Therefore, a comprehensive medical and psychosocial approach using a collaborative care model might help to reduce the impact of the disease to patients, caregivers and society.

COPD is a potential risk factor for developing cardiovascular disease. However, the mechanisms it develops less clear. The potential postulated mechanism is most likely because of complex interaction of systemic inflammation, hypoxia, sympathetic activation, oxidative stress and physical inactivity.

Depression and anxiety are common in patients with COPD and asthma. They are often under-recognized and under-treated. Therefore, healthcare professionals should play an active role to identify these psychiatric disorders using screening tools during routine consultations.

Current evidence suggests that simply offering antidepressant drug therapy for COPD patients with depression is not an effective method to treat this patient group. Collaborative care model which involve patients in self-management programme is worthy of consideration.

The role of systemic inflammatory markers in the pathogenesis of depression and cardiovascular disease in patients with COPD are worthy of exploration.

COPD is a risk factor for developing lung cancer. It is important to assess high-risk COPD patients periodically for lung cancer in order to provide appropriate early curative intent intervention.

Conclusion

The impact of comorbidities on COPD and asthma patients' quality of life and healthcare utilization is most likely to be enormous in the next few years. Therefore, it is important to screen patients for comorbidities and monitor regularly for potential side effects after a change in health status or a significant lifetime event (e.g. after loss of a job or loss of the loved ones). Those identified with clinically

depression should be treated promptly with appropriate pharmacological (antidepressant drug therapy) and non-pharmacological therapy (including exercise therapy and cognitive behavioural therapy).

The findings of this review highlight factors that contribute to cardiovascular diseases, lung cancer and major depressive episodes in patients with COPD are multifactorial. The majority of COPD patients are most likely from the disadvantaged lower socio-economic status, who are prone to high psychosocial morbidity, e.g. elevated active smoking, overweight status and low physical inactivity. Therefore, the time has come for close collaboration between secondary/tertiary healthcare providers and primary healthcare and social care services to mobilize resources and devise innovative long-term public health initiatives, for example, smoking cessation and obesity in order management to reduce the burden of lung cancer, cardiovascular diseases and depression to the wider society.

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Chapter 10
Non-pharmacological Interventions to Manage Depression and Anxiety Associated with Chronic Respiratory Diseases: Cognitive Behavioral Therapy and Others

Minna J. Hynninen, PhD and Inger Hilde Nordhus, PhD

Introduction

Chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and asthma, are not only characterized by physical burden and disability, but may also involve significant changes or challenges in daily activities, social relationships, self-perception and emotional functioning. The physical symptoms that are persistent in nature and the degenerative trajectories of disease contribute to psychological responses that impact the patients' quality of life [1]. Some patients seem to adapt well to living with a chronic respiratory disease, while others respond with anxiety or depression. Although a high prevalence of anxiety and depression in chronic respiratory diseases and their subsequent impact on physical health outcomes have been documented [2–4], the psychological comorbidities often go untreated or inadequately treated [5]. Relatively, few studies have examined how these comorbid conditions should preferentially be treated [6], and thus, it is not surprising that there has been little attention to the management of mental health problems in clinical guidelines for treating chronic

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respiratory diseases [7]. While any strategies that can relieve symptoms of anxiety and depression will ultimately be of benefit to patients, lately there has been a growing interest in the non-pharmacological interventions [8].

Non-pharmacological approaches to managing anxiety and depression in chronic respiratory diseases have typically involved pulmonary rehabilitation and cognitive behavioral therapy (CBT), or variants or components of these, such as education, self-management programs or relaxation. Based on experiences with other chronic diseases, other potentially effective treatments for reduction of depression and/or anxiety symptoms have been proposed, including interpersonal psychotherapy, supportive therapy and self-help groups [7]. *Interpersonal psychotherapy* links the patient's mood to disturbing life events that either trigger or follow from the onset of the mood disorder, and the patient's task in therapy is to resolve the disturbing life event, by building social skills and organizing his or her life [9]. In *supportive therapy*, techniques from a range of therapeutic paradigms (e.g., psychodynamic, cognitive behavioral, interpersonal psychotherapy) may be used to restore or maintain psychological health and functioning [10]. *Self-help groups* or *patient support groups* are structured around mutual help and social support, aiming at increasing self-esteem, self-efficacy and positive emotions [7, 11]. However, the efficacy of these interventions for patients with chronic respiratory diseases remains largely unknown [7]. Although systematic reviews of non-pharmacological interventions for anxiety and depression in the patient group have reported problems with insufficient data and low-quality studies, they generally conclude that CBT and comprehensive pulmonary rehabilitation show some promise [12–15].

Pulmonary rehabilitation is an evidence-based, multidisciplinary intervention, which typically involves assessment of patient's problems and goals, education, exercise, nutritional intervention and psychosocial support. It is an integral part of the clinical management of chronic respiratory disease, aimed in particular at patients who remain symptomatic or continue to have decreased function despite standard medical treatment. A meta-analysis by Coventry and Hind [15] concluded that programs comprising exercise, education and psychosocial support reduce anxiety and depression in patients with COPD, and there is growing evidence that outpatient comprehensive pulmonary rehabilitation reduces anxiety and depressive symptoms in the patient group significantly, compared to standard community care [16]. It is, however, unclear which components of pulmonary rehabilitation have the greatest impact upon anxiety and depression [17]. Coventry and Hind [15] state that although education is a key part of a successful pulmonary rehabilitation program, education alone is insufficient to improve mental health symptoms. Exercise may improve self-efficacy and have a desensitizing effect on symptoms of anxiety [18]. On the other hand, there is also some evidence suggesting that exercise without a psychological intervention does not improve anxiety and depression [19]. Adding progressive muscle relaxation to a program that already includes psychosocial support does not seem to improve the outcome [20].

Although only a few studies have examined whether pulmonary rehabilitation is effective in reducing clinically significant symptoms of anxiety and depression, it appears that also patients with more severe psychological distress can benefit from pulmonary rehabilitation [21, 22]. However, long-term effects may be more difficult to

achieve, and the psychological benefits tend to decline rather rapidly after completing the program [16]. It has been suggested that structured, psychological interventions that help the patients to sustain positive health behavior over time, such as CBT or motivational interviewing, are needed to improve the patients' self-management skills [23] and to maintain the psychological benefits of pulmonary rehabilitation [16]. Like CBT, *motivational interviewing* is an established, goal-oriented psychological intervention that can produce positive behavioral change in the context of chronic illness [24], but its effectiveness for patients with chronic respiratory disease is currently unknown [16].

In the following, we will focus on the role and potential of CBT for managing comorbid anxiety and depression in chronic respiratory diseases. Most of the literature on the psychological comorbidities in chronic respiratory diseases relates to COPD and asthma, and consequently, our main focus will be on these diseases.

Cognitive Behavioral Therapy (CBT)

According to the cognitive behavioral model, mental health problems arise when people exhibit maladaptive patterns of thinking and behavior that influence their mood and emotional experience. Interplay between negative thoughts, maladaptive behaviors, physical symptoms and highly charged emotions is assumed to cause and maintain patients' symptoms and problems (Fig. 10.1). CBT interventions draw on empirically based cognitive and behavioral theoretical models to support the use of specific treatment techniques and processes, in order to address negative patterns in thoughts and behavior that maintain or contribute to psychological distress. Treatment is goal-oriented and based on a structured procedure, and often time-limited.

Research shows that CBT can be equally efficacious as psychotropic medications in treating mental health symptoms (e.g., [25]), and the effect of CBT may be more enduring than the effect of medications [26]. Large effect sizes have been reported for CBT for depression and anxiety disorders [27], and there is evidence suggesting that CBT is a robust treatment also in group format [28].

Cognitive theories of depression suggest that specific maladaptive thinking patterns increase individuals' likelihood of developing and maintaining depression when they experience stressful life events [29]. Individuals who are vulnerable to

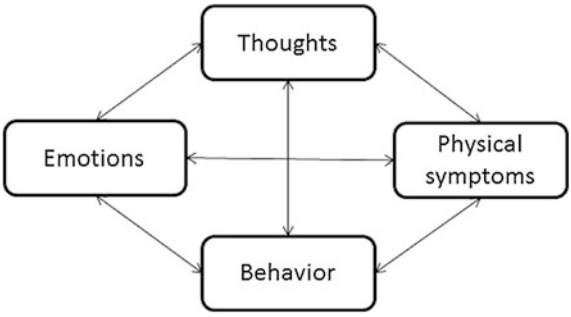

Fig. 10.1 CBT model

depression tend to engage in negative information processing and view themselves, their environment, and the future in a pessimistic light. In the cognitive domain, the treatment is directed at teaching and applying cognitive restructuring techniques so that the negatively distorted thoughts causing depressive mood can be corrected and replaced by more adaptive thinking. According to behavioral theory, depressed individuals do not get enough positive reinforcement from interactions with their environment to maintain engagement (e.g., [30]). The less they pursue activities and social interactions that they usually enjoy, the more they experience depressive symptoms such as lack of energy and anhedonia. Within the behavioral domain, techniques such as activity scheduling or skills training are used to remediate passivity and social isolation that contribute to depression.

Cognitive theory proposes that dysfunctional thinking is also associated with the development and maintenance of anxiety disorders, and the way we think about a potential threat can cause anxiety and worry [31]. The maladaptive thought patterns of individuals with anxiety tend to revolve around overestimation of potential threat or danger, catastrophizing, or underestimating one's ability to cope with adverse situations. There are a variety of factors that may contribute to a first episode of anxiety, such as a traumatic event, unpleasant physical symptoms of a somatic illness, stress or physiological arousal as a consequence of sleep deprivation or illness. According to the behavioral perspective, fear conditioning may take place when individuals respond to an uncomfortable experience with significant anxiety. During fear conditioning, previously neutral stimuli (e.g., elevated heart rate) become associated with a perception of threat and a fear response [32]. Dysfunctional thinking is often the conscious reaction during this process, and as the anxiety disorder develops, catastrophic cognitions will contribute to its maintenance.

Anxiety is maintained or exacerbated when people avoid encounters with the stimuli associated with anxiety, or even thoughts of situations or stimuli that are anxiety provoking. Avoidance, which may also include behaviors such as use of tranquilizers or alcohol, may reduce symptoms in short term, but it also keeps the fear response intact. In addition to cognitive restructuring of dysfunctional thoughts, a CBT intervention for anxiety also typically includes exposure training to the feared stimulus or situation. The exposure needs to be long enough for the anxiety and fear to be reduced, so that the patient realizes that feared consequences do not occur or that anxiety can be tolerated. For the exposure to be successful, it is also important to identify and change more subtle attempts to avoidance or defensive, safety-seeking behaviors during the training, such as carrying a medicine bottle or staying close to a familiar person [31–33]. In addition to exposure, other behavioral components may include relaxation training, meditation or breathing exercises for decreasing physiological arousal. These techniques can also serve as coping strategies that help the patient to tolerate anxiety.

During the initial sessions of CBT, the therapist works to motivate the patient to change and to help the patient to understand the treatment model and structure. Forming a positive working alliance with a shared understanding of treatment goals and process serves as a basis to implement the cognitive and behavioral interventions. Psychoeducation aiming to inform the patient about the actual mental health

symptoms and the specific focus of the subsequent treatment approach is an important part of this stage. Based on the initial assessments and the patient's presenting problem, the therapist develops a case formulation that will help to select and refine the interventions for a meaningful treatment plan.

Understanding Anxiety and Depression in Chronic Respiratory Disease: A Cognitive Behavioral Perspective

Traditional CBT model of anxiety is based on the premise that individuals with anxiety overestimate the likelihood or impact of negative outcomes [31], which leads to maladaptive coping behaviors such as avoidance. Patients with chronic respiratory disorders differ crucially from physically healthy persons with anxiety, in that their health and breathing are objectively threatened [34]. They are often subjected to several risk factors for anxiety and depression, such as functional limitations, lack of control over life circumstances, psychosocial losses and serious life events. Certain specific characteristics of respiratory disorders may also increase the risk of developing anxiety or depression and predispose the patients for these conditions. In patients with COPD, some of the symptoms of the lung disease, such as shortness of breath, lack of energy, chest pain and sleep problems, overlap and thus may also interact with symptoms of anxiety and/or depression. Dyspnea is a central symptom of both anxiety and respiratory disease, and there is evidence indicating that emotional distress contributes to dyspnea, which may cause a loss of breathing control and, in turn, lead to panic [35]. COPD patients also typically suffer from fatigue, and depressive mood may lower the level of energy even further and lead to passivity, which again may exacerbate physical deterioration [36].

Figure 10.2 summarizes the CBT model of anxiety and depression in chronic respiratory diseases.

Although persons with chronic respiratory disorders face very real challenges and adversities, the experience of symptoms, such as dyspnea, is subjective, and therefore ambiguous and open to catastrophic or overly negative interpretations. Applied to chronic respiratory disorders, the cognitive model suggests that patients with anxiety or depression would experience more catastrophic and negative cognitions about their respiratory symptoms compared to patients without anxiety or depression [37]. Support for this model comes mainly from studies that have found higher levels of catastrophic cognitions in respiratory patients who experience panic anxiety, compared to those who do not [38, 39]. Findings by Gurney-Smith et al. [37] indicated that severity of illness-specific catastrophic cognitions predicts the level of anxiety triggered by COPD symptoms, as well as behavioral avoidance in unsafe situations. Other studies have also demonstrated that heightened dyspnea perception and misinterpretation of physical sensations are associated with panic disorder in COPD, independently of respiratory function [40, 41].

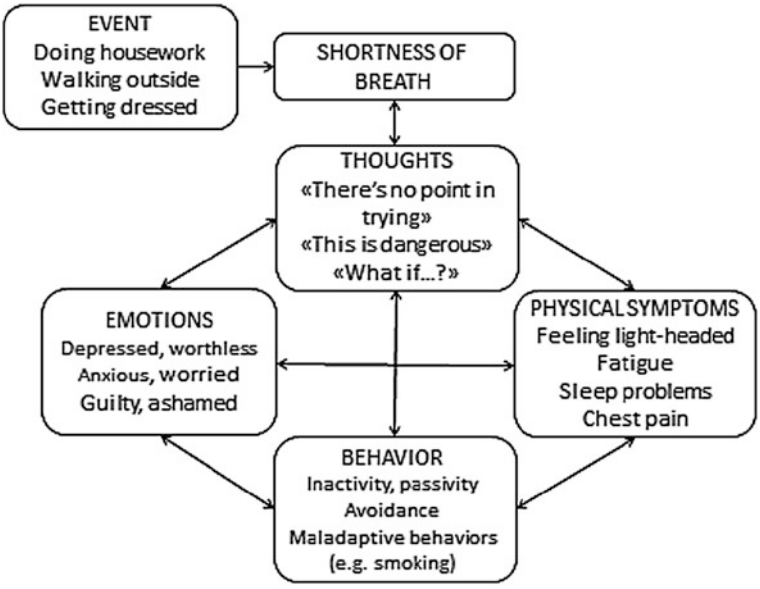

Fig. 10.2 CBT model of anxiety/depression in chronic respiratory disorders

Although catastrophic cognitions may be more frequent in patients with panic attacks, or they may accentuate the attacks, they do not necessarily have a causal role. Bouton et al. [42] have proposed that panic disorder develops because exposure to panic attacks causes the conditioning of anxiety to internal or external cues. Individuals with panic disorder also develop anxiety focused on the next potential panic attack, and perceive the attacks as uncontrollable and unpredictable. In respiratory patients, the extremely frightening feeling of breathlessness and suffocation during dyspnea may lead to conditioning of anxiety to internal and external cues associated with dyspnea. Bouton et al. [42] predict that treatment approaches entailing extinction or exposure to conditioned stimuli will most likely be successful.

In addition to panic attacks or more acute episodes of intense anxiety, the cognitive behavioral perspective can also be applied to generalized anxiety and depression in patients with chronic respiratory disease. Fear and avoidance of symptoms of the respiratory disease may result in considerable modifications in lifestyle and attempts to avoid exertion, which then may become a constant source of worry [43]. Eventually, these processes may contribute to more or less constant feelings of anxiety and/or depressive mood.

According to the CBT model, generalized anxiety disorder stems from perceptions of the world as a dangerous place, which lead to maladaptive and habitual cognitive, behavioral and physiological responses [44]. The patients commonly exhibit an attentional bias to threat cues, worrisome thinking, and subtle behavioral avoidance and slowed decision making, as well as excessive muscle tension and an

autonomic inflexibility [44, 45]. Patients with chronic respiratory disorder, fearing dyspnea, are often attentive to all potential threats and situations that may cause breathlessness, and they may also spend considerable time planning ahead to avoid exertion, as well as worry about things that may go wrong. In a qualitative study, COPD patients described how planning of daily activities was seen as necessary to control breathlessness, and how it was also associated with worry about trivial things and limited their ability to participate in social activities [43].

Restriction of activity because of functional limitations and fear of respiratory symptoms are likely to lead to loss of pleasurable experiences and social withdrawal, which can be linked to increased levels of depressive mood. Patients also typically suffer from fatigue, and depressive mood may lower the level of energy even further and lead to increased passivity, which again may exacerbate physical deterioration [36]. As a part of the vicious circle of depression-related activity avoidance and deconditioning, isolation and passivity will also influence the patients' self-esteem and contribute to more negative thoughts about the self, the environment, and the future. In COPD patients, depression has been linked to loneliness, and it is also inversely related to coping by seeking social support [46, 47].

CBT for Patients with Chronic Respiratory Disorders

While the CBT treatment for depression and/or anxiety can in many ways be similar when treating patients with or without chronic respiratory disease, there are also some special issues that need to be taken into consideration. Because there is some overlap between symptoms of respiratory disorders and anxiety and depression, a comprehensive approach to assessing both somatic and psychological symptoms is necessary before the CBT intervention. A focus on anxiety or depression should not go at the risk of ignoring progression in the respiratory disease. Although anxiety may contribute to breathing problems and other respiratory symptoms, an exacerbation of the respiratory disease or increase in symptoms as a consequence of disease progression can also be a significant source of anxiety. Complaints of poor sleep, a common symptom in anxiety and depression, can also be caused by fatigue or pain as a consequence of progressing respiratory disease, or by other, comorbid sleep-related disturbances that need to be treated [48]. Thus, a thorough and multifaceted assessment may be required in order to select the right target for treatment and optimize the medical treatment for the respiratory disease. Because of the symptom overlap, the therapist also needs to be competent in distinguishing psychological symptoms from physical symptoms during the treatment.

In the beginning of the CBT intervention, in addition to educating patients about the mental health symptoms and the treatment approach, the psychoeducation should include specific elements about the respiratory disease, and how the symptoms of the respiratory disease may interact with symptoms of anxiety and depression ("Being anxious can make your breathlessness feel worse"). The goal is to become aware of dyspnea- or depression-related vicious circles, with activity

avoidance, deconditioning and more respiratory symptoms ("Avoidance of exertion will lead to reduced fitness, maintenance of fear and low mood, which again can make your breathlessness worse"). Patient's misconceptions or unhelpful beliefs ("Breathlessness is always dangerous or harmful"), and maladaptive patterns of behavior related to the respiratory disease (e.g., overuse of inhalators, emergency admissions to hospital because of anxiety) can be assessed and addressed at the same time [49].

Exploring the patient's current lifestyle and limitations as well as expectations for the future can be helpful, in order to shape and adapt the therapy for the patient's needs. The therapist should also encourage the patient to start monitoring his or her psychological symptoms (physical symptoms, thoughts, feelings and behavior), and help the patient to differentiate between respiratory symptoms and anxiety or depression ("Am I breathless because of an exacerbation or is it because I feel anxious?").

Other components included in the CBT treatment should be based on the initial case formulation. A case formulation is the summation of the clinician's understanding of how the patient's problem develops, perpetuates and evolves over time. Based on this understanding, specific interventions aimed at reducing the impact of causal and/or maintaining factors are planned [50]. Since patients with chronic respiratory disorders often suffer from mild to moderate, mixed symptoms of both anxiety and depression, rather than having a "pure" depressive or anxiety disorder, an approach that incorporates components for treating both anxiety and depression can be chosen (e.g., [51]). However, more severe psychiatric disorders, such as panic disorder, are likely to require targeted interventions [34].

In patients with chronic respiratory disorders, common causal or maintaining factors for anxiety and depression are passivity and avoidance behaviors, such as avoidance of exertion and anxiety-provoking activities and situations. Avoidance behaviors can be challenged by graded exposure or behavioral experiments, whereas goal setting, activity scheduling and pacing activities can be effective approaches to counteract passivity and inactivity. The patient may devise a list of activities or situations that they either avoid or wish to do, and create an activity hierarchy with easy activities or situations on the top of the list and more difficult ones at the bottom. The therapist helps the patient to choose appropriate activities and make concrete, step-by-step plans for homework assignments, breaking more complex or difficult tasks into achievable and realistic goals. Patients who are mainly suffering from anxiety and anxiety-related avoidance can be encouraged to choose exposure tasks, whereas pleasurable activities that will improve mood can be scheduled for patients with mainly depressive symptoms. For exposure tasks, realistic goals need to be set and the exposure program should be developed in consultation with patient's respiratory physician, taking into account patient's current health and stage of illness [34].

Pacing activities and alternating planned periods of activity with regular rest periods may be necessary with some patients, in order to avoid that the patient pushes himself or herself to do too much, and ends up having to rest for a long time to recover. Teaching coping skills to manage symptoms of anxiety and depression, such as relaxation, breathing techniques and attention management (e.g., distraction),

is also often helpful and necessary before the patient can be expected to face their fears in exposure tasks or increase their activity levels. In CBT for anxiety in healthy individuals [52, 53], safety behavior is considered to be countertherapeutic, providing only temporary relief from symptoms, and safety-seeking behavior may also eventually be a maintaining factor in persisting anxiety. Although activity pacing and breathing techniques can be characterized as safety behaviors, in chronic respiratory disorders they are an important method for self-management of dyspnea [54], and the treatment may be less focused on extinguishing safety behaviors than on teaching effective coping skills. The aim is to seek a balance between some degree of control over breathlessness and other respiratory symptoms, while also increasing tolerance and reducing the fear of symptoms.

Patient's unhelpful beliefs, maladaptive thought patterns or catastrophic thinking that may contribute to anxiety and depression, as well as maintain passivity and avoidance, could be addressed with cognitive restructuring. Cognitive restructuring is a set of techniques for becoming more aware of thoughts and for modifying them when they are maladaptive or unhelpful. The aim is to use reason and evidence to replace thought patterns that are overly negative ("I can't do anything anymore, I am hopeless!") or anxious ("What if I become breathless and can't get any help?") with more accurate and functional alternatives ("I may not be as quick and strong as I used to be, but I can do this, one step at a time"; "I may not be able to avoid breathlessness altogether, but I will be okay").

When it comes to chronic respiratory disorders, some degree of anxiety about the respiratory symptoms can be adaptive and motivate the patient for appropriate action, such as using preventive medication. Conversely, low level of illness-related anxiety may be associated with ignoring symptoms and delaying use of symptom relievers, and with a coping style associated with denial of the disease, which is unfavorable for good disease management [55]. However, a constant worry and focus on the symptoms is neither adaptive nor helpful, and worrying also has tendency to occur at inappropriate times, e.g., when trying to get to sleep at night. With patients who are overly attentive to physical symptoms or who constantly worry about their symptoms and things that may go wrong, distraction or worry postponement techniques are sometimes used. Distraction can be helpful as a short-term tool in overcoming a brief anxiety-inducing situation, but it is generally recognized that using distraction as a long-term coping strategy often makes symptoms worse and is not a cure for anxiety. Distraction by focusing one's attention to the present moment (e.g., sensory experience, the task one is engaged in) can, however, also help to "postpone" worries. Postponing worries to a chosen time and place is often easier than suppressing them completely ("I'll think about this later, now is not the right time"), and it can also lead to either dismissal of worries as unimportant or to more constructive problem solving during the chosen "worry time."

Other components, such as sleep skills or problem-solving skills, may be included in the intervention according to the patient's needs. See Table 10.1 for an overview of key components in CBT treatment for anxiety/depression in chronic respiratory disorders (e.g., [51, 56]).

Table 10.1 Key components of the CBT intervention

Component	Aim	Example
Psychoeducation/awareness	Increase awareness of how COPD may affect psychological well-being, and how psychological symptoms and behavioral patterns associated with anxiety and depression may add to the burden of the lung disease	Explaining how dyspnea may set off panic anxiety, and how anxious thoughts or catastrophizing about physical symptoms may contribute to dyspnea
Relaxation	Use breathing exercises for relaxation and coping with physical symptoms	Practicing relaxation with diaphragmatic breathing when feeling anxious, or coping with breathlessness with pursed lip breathing. Imaginal exercises can be used to facilitate practice in real-life situations
Cognitive restructuring	Identify and challenge depressive patterns of thought or anxiety-related rumination/fearful thoughts, and explore more functional patterns of thought	*Depressive thought pattern*: blaming self for being ill and not being able to take care of house and family *More helpful thought*: "I am doing my best under the circumstances and I can ask for help when I need it."
Behavioral activation	Identify depressive, passive behaviors and replace them gradually with activities that are pleasant and/or increase one's sense of mastery	*Depressive pattern*: staying at home, avoiding contact with other people, ruminating about past failures *Behavioral activation*: making a plan to go for a walk three times a week with a neighbor
Graded exposure	Replace avoidance of anxiety-provoking situations and activities with graded exposure, in order to increase tolerance and reduce anxiety	*Fear-based avoidance*: any activity that may cause breathlessness, such as walking up stairs or walking outside *Exposure*: going for a short walk with a trusted friend or family member. Planning ahead and practicing breathing techniques. Increasing the distance gradually, and eventually going for a walk alone

CBT for Chronic Respiratory Disorders: Challenges and Possibilities

Systematic reviews evaluating the efficacy of CBT for anxiety and/or depression in chronic respiratory disorders have been unable to draw firm conclusions, due to a low number of CBT treatment trials and small sample sizes [12, 13] or heterogeneity and low quality of the trials [57]. Although the overall conclusion is that further research on the efficacy of CBT is needed, in more recent randomized controlled trials CBT in individual format has been superior to usual care for anxiety and depression in patients with COPD [58, 59] or asthma [60]. CBT in group format has also improved symptoms of anxiety and depression in COPD patients significantly, and it has been superior to usual care [56] but not to patient education [61, 62].

Discussing their findings, Kunik et al. [62] suggest that both CBT and patient education may have increased patients' self-efficacy, which could partly explain the decreased anxiety and depression in both groups. Furthermore, although the group format has obvious benefits in terms of greater efficiency with regard to therapists' time, it also requires that all patients are instructed in the same skills and receive the same information. In another study, group CBT reduced anxiety and depression and was superior to usual care, but many study participants were still suffering from clinically significant symptoms at the end of the intervention period [56]. These findings underline the need for exploring further options that could improve the outcomes. More idiographic treatment, based on individual case formulations, could be beneficial in terms of more emphasis on individually appropriate techniques and treatment components.

Integrating mindfulness- and acceptance-based interventions to CBT treatment could also potentially improve outcomes. Mindfulness-based programs are today widely available, and have been shown to reduce mental health symptoms, as well as disease-related distress and medical symptoms in a range of chronic diseases [63–65]. With mindfulness practice, patients learn to experience previously avoided thoughts, feelings and sensations non-reactively and without judgment, one's present experience is allowed to be "just what it is." The practice may thus function as a reciprocal inhibition/behavioral exposure, as it changes the response tendency from avoidance to observation of the "here-and-now" experience [66]. By developing the capacity for self-regulation of attention, mindfulness may also reduce the tendency to worry or ruminative thought, while the emphasis on non-judgmental acceptance can promote an attitude of self-compassion in contrast to guilt and shame.

Currently, CBT interventions are not widely available, and a shortage of trained CBT practitioners is also a common problem. Computerized and telephone-delivered CBT have been suggested as alternatives [12], while Heslop et al. [49] argue for the potential value of CBT training for specialist nurses from a non-psychology/psychiatry background working in chronic disease management. According to them, dual training allows the therapist to deliver patient education

and CBT in parallel, and direct the treatment appropriately. Respiratory nurses with CBT training can also deliver the treatment in normal outpatient care, and patients can undergo therapy in settings with which they are familiar and avoid the stigma that is sometimes associated with attending a mental health specialist.

CBT components can also be integrated into pulmonary rehabilitation programs relatively easily and be helpful for a wide range of patients. Psychoeducation and increased awareness of the role of psychological symptoms in chronic respiratory disease are likely to be useful knowledge for all patients. Breathing retraining is a common component in the programs, and patients can benefit from learning how to use breathing techniques and exercises to relax and manage anxiety. Similarly, the role of exercise and activity in improving psychological health and reducing anxiety-related patterns and depressive avoidance can be explicitly emphasized in the programs. Regular physical exercise during pulmonary rehabilitation can also provide a method for systematic exposure to experiencing and managing dyspnea, which is likely to reduce dyspnea-related anxiety [34]. Patients with clinically significant anxiety and/or depression are, however, likely to need more individualized attention and counseling. A small, randomized trial indicates that combining psychotherapy with rehabilitation can give additional benefits and reduce anxiety and depression, compared to pulmonary rehabilitation alone [19]. Although pulmonary rehabilitation may be an ideal setting for introducing more intensive psychological treatment for the majority of patients [7], for those with chronic or more severe psychiatric disorders referrals to mental health specialists are likely to be the best option.

In pulmonary rehabilitation as well as in CBT trials, problems with non-attendance and drop-out have been described [62, 67]. Patients who have problems with transportation or mobility, or have more severe health impairment are often absent in these settings [56, 62]. Problem-solving skills training to address behavioral limitations as well as access to a health-care coordinator who can identify and overcome the specific barriers have been suggested as strategies for dealing with these challenges [68, 69].

Most patients with stable respiratory disease are managed in primary care, and evidence-based care programs that address mental health are needed also in primary care settings [7]. *Collaborative care* has been extensively investigated in primary care settings, also with elderly patients [70], and it involves using a depression care manager who coordinates the various aspects of care. Although the approach may be harder to standardize than CBT, it is likely to be more accessible [17].

Pommer et al. [6] have also described a stepped care, *disease management* approach to comorbid anxiety and depression in primary care patients with asthma or COPD. The approach comprises four core elements: systematic screening of anxiety and depression, treatment in case of positive screening, monitoring of symptoms and intensified treatment for patients who remain symptomatic. The treatment starts with four sessions of psychoeducation of anxiety and depression in COPD or asthma, and the rationale of CBT is provided, alongside with practical coping tools for the symptoms. In case of non-remission, step two consists of a course on coping with anxiety and/or depression, depending on what the patient

needs. Main components of the course involve cognitive restructuring, behavioral activation, social skills training and relapse prevention. Patients with recurrent symptoms will enter step three, with coaching together with optional antidepressant and/or anxiolytic medication, and will receive booster sessions from step two. The effectiveness of the disease management approach is being tested in a randomized controlled trial, compared to usual asthma/COPD care.

Summary

In this chapter, we have provided an overview of non-pharmacological management of comorbid anxiety and depression in chronic respiratory disease, with emphasis on CBT. Although both comprehensive pulmonary rehabilitation and CBT have shown potential as treatment models, more research is needed to delineate the most beneficial components, to improve the effectiveness and to overcome the barriers for treatment.

While many of the CBT components for treating depression and/or anxiety are similar when treating patients with or without chronic respiratory disease (e.g., cognitive restructuring, behavioral activation), there are also some special issues that need to be taken into consideration because of the symptom overlap between respiratory disorders and anxiety and depression, and the disease-related limitations to health and functioning.

CBT treatment is not currently easily available to all patients, but some of its components can be easily integrated into pulmonary rehabilitation programs. Considering the close associations between anxiety, depression and respiratory symptoms, a comprehensive, multidisciplinary approach that addresses the complex web of medical illness, disability and psychological distress is likely to be optimal for most patients. More intensive psychological treatment may be required with increasing severity of the psychological symptoms, either in combination with pulmonary rehabilitation or by referrals to mental health specialists.

Access to a health-care coordinator has been suggested as a way to overcome barriers for treatment. CBT-based, stepped-care treatment programs can also be implemented in primary care settings and eventually combined with antidepressant or anxiolytic medication. By integrating mental health care into the overall medical regimen, it may also be easier to reach more patients who are suffering from psychological distress.

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Chapter 11
Pharmacological Therapy and Anxiolytics in Patients with Respiratory Diseases

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of disability, morbidity and mortality in old age. The World Health Organization estimates that over 200 million are living with COPD worldwide [1, 2, 3]. Studies [2, 4] report that over two-thirds of people with COPD patients are two or more comorbidities that interfere with their activities of daily living (ADL). The most common symptoms in moderate-to-severe COPD patients include breathlessness with minimal exertion and excessive fatigue which are associated with a reduction in the ability to undertake activities of daily living (ADLs). Some of the most common comorbidities are depression and anxiety disorders which represent an increasingly greater burden as the person with COPD ages and respiratory symptoms become worse. Elkington and co-workers [5] found that at the end-stage COPD (i.e. the last phase in the course of the progressive disease) 98% of patients exhibited breathlessness 'all the time', which persisted at rest or minimal exertion despite receiving optimal treatment. In addition, the other symptoms at this stage included excessive tiredness, low mood and pain ('some or all the time') reported by 96, 77 and 70% of respondents, respectively. Other studies have reported that people with advanced-stage COPD are more breathlessness than those with advanced lung cancer [5, 6]. Furthermore, health-related quality of life has been reported as comparable to or worse than in advanced non-small-cell lung cancer patients [6].

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A recent systematic review [7] reported the prevalence of depression to range from (8–80% and 6–74% of anxiety) symptoms in COPD patients compared with chronic heart failure (CHF) (10–60% depression; 11–45% anxiety), respectively. Furthermore, the psychological burden of clinical depression may be as high as 90% in advanced COPD patients compared to 52% with non-resectable non-small-cell lung cancer patients [6]. Those with COPD and comorbid depression are less likely to engage in many social activities and are frequently isolated and housebound because of increased physical disability and fear of breathlessness. In addition, in this group, depression can interfere with self-management and adherence to medical treatment.

For these reasons, diagnosing and treating comorbid depression is crucial. Antidepressants and anxiolytics are widely used in older adults [8, 9]; however, the efficacy of these drugs in people with advanced-stage COPD to treat moderate-to-severe depression, breathlessness and pain has not been adequately examined [10, 11]. The aim of the review is twofold: (1) To examine the efficacy of antidepressants drug therapy in patients with COPD and major depression and (2) to examine the safety of benzodiazepines and opioids (anxiolytics) in patients with severe respiratory disease with advanced-stage of COPD. It will also provide clinical tips to improve the management of depression, breathlessness and pain in patients with COPD.

Antidepressants Drug Therapy in Patients with COPD

Untreated and undiagnosed major depression in patients with COPD may lead to a greater burden of an increase in physical disability, poorer adherence to medical treatment, lower self-esteem and social interaction, more impaired quality of life and greater healthcare utilisation compared to COPD patients without major depression [12, 13]. Therefore, the optimisation of medical treatment for COPD in conjunction with the selection of appropriate antidepressants while minimising drug interactions is important.

The National Institute for Clinical Excellence (NICE) recommends the use of antidepressants in the treatment of major depression for patients with chronic diseases in both primary and secondary care settings [13]. Furthermore, NICE guidelines recommend selective serotonin reuptake inhibitors [SSRIs] as a first line of treatment choice in the acute phase of treatment for patients with major depression. SSRIs have better safety records and fewer side effects compared to older antidepressants such as tricyclic antidepressants. This review focuses primarily on antidepressant drug trials that have been conducted in patients with COPD and major depression.

Selective Serotonin Reuptake Inhibitors (SSRIs)

There are only seven studies that have been conducted using the SSRIs in the treatment of major depression in patients with COPD [14], and all are having

relatively small sample sizes and some methodological limitations. The summary of the main findings will be reported here. For a detailed review, the reader is referred to Yohannes and Alexopoulos paper [14].

Sertraline

Smoller et al. [15] conducted a non-randomised, open-label pilot study ($n = 6$) which examined the efficacy of sertraline over a 6-week period, with initial dose of 12.5 mg daily increasing to 100 mg within the first two weeks. There was no significant improvement in depressive symptoms and signs, or physiological measures of COPD such as lung function test. However, 5 out of the 6 COPD patients showed some improvement in their daily activities. A retrospective study [16] by Papp and co-workers explored the effectiveness of sertraline at a daily dose ranging from 25 to 100 mg in seven patients with chronic obstructive pulmonary disease for the treatment of comorbid depression. They observed significant improvement in dyspnoea scores in all seven COPD patients. A few patients had shown some improvement in exercise capacity, depression and anxiety. In addition, the authors have investigated the potential antidepressants effect on physiological parameters or not. However, no improvement was observed in forced expiratory volume in one second (FEV_1). A recent study by He and co-workers [17] examined the efficacy of Sertraline hydrochloride 50 mg/day for 6 weeks [$n = 60$] compared to the placebo group [$n = 60$] receiving dummy pills. Depression was diagnosed using the 17-item Hamilton Depression Rating Scale. They showed statistically significant improvement in quality of life, reduced depressive symptoms and increased in exercise capacity in the intervention group compared to the placebo. The findings are encouraging, but 6 weeks of Sertraline treatment was insufficient to assess the long-term effect to full remission. Thus, a longer term treatment and follow-up is required.

Fluoxetine

Evans and co-workers conduced an 8-week randomised, double-blind trail comparing the efficacy of fluoxetine 20 mg daily to that of placebo in 42 elderly inpatients with depression and respiratory diseases including COPD diseases [18]. Sixty-seven per cent of patients in the fluoxetine group, compared to 37% of those in the placebo group, had an improvement in depression rating scores (defined as a 50% reduction in the 17-item Hamilton Depression Rating Scale (HDRS) and/or a final score of 10 or less [18]. However, this difference in response rates between the two groups did not meet statistical significance and there was no difference between groups in lung function scores. This might be due to small sample size, which led to type 1 error.

In a single blind study, Yohannes et al. [19] examined the efficacy of fluoxetine 20 mg daily over six months. Major depression was diagnosed using the Geriatric Mental State Scale [20]. Fourteen depressed COPD patients commenced the fluoxetine therapy, and (n = 7) completed the study. Five patients withdrew because of adverse side effects (intolerable tremor, feeling lethargic, agitation and nightmares), 1 withdrew due to family problems, and 1 died due to unrelated cause. Of those who completed the study, 4 responded to fluoxetine (50% reduction in the Geriatric Mental State scale score). There was no significant improvement in forced expiratory volume in one second (FEV_1), quality of life (measured by the Breathing Problems Questionnaire) and physical activity scores after 6 months of fluoxetine therapy.

Paroxetine

A relatively small, double-blind, randomised controlled trial [21] examined the efficacy of paroxetine 20 mg daily over 12 weeks in advanced stage of COPD patients with comorbid depression. Twenty-three participants were randomised. Of these, 15 participants (8 paroxetine and 7 placebos) completed the study. A clinically significant difference favouring paroxetine was observed in quality of life, measured on the chronic disease respiratory questionnaire, especially in 'mastery' and 'emotional function'. There was some improvement in dyspnoea and fatigue scores in the paroxetine group, but this did not reach statistical significance. Notably, as was seen with the fluoxetine studies mentioned above, almost one-third of the participants discontinued treatment due to adverse side effects. Eiser and colleagues compared the efficacy of paroxetine (20 mg daily) against placebo over 6 weeks in 28 patients with COPD [22]. There was no statistically significant difference between the two groups in exercise capacity, lung function and quality of life. Paroxetine was un-blinded after 6 weeks, and both groups continued on open-label paroxetine 20 mg daily. A statistically significant improvement in depression scores, walking distance and quality of life was observed three months later.

Tricyclic Antidepressants (TCA)

To date, only four randomised double-blind studies have investigated the efficacy of TCAs in people with COPD [23–26]. Again, because of the low sample sizes of the trials and high dropouts of participants from these studies, briefly the summary of main findings for each of several TCAs will be reported here [14].

Desipramine

An 8-week, placebo-controlled study [23] examined the efficacy of desipramine in 13 people with stable COPD as defined as no hospital admission in the previous

6 weeks due to acute exacerbation of COPD) and depression. Desipramine was started at a dose of 25 mg daily and increased weekly to a target dose of 100 mg. Six participants completed the trial. Both groups had similarly improved depression scores using the Beck Depression Inventory (BDI), and no significant difference in physiological outcomes was noted.

Doxepin

Light and co-workers examined the efficacy of doxepin in 12 outpatients with COPD and depression in a randomised placebo-controlled trial [24]. In this 6-week study, doxepin was started at a dose of 25 mg daily and increased as tolerated with a maximum dose of 105 mg daily. Three patients withdrew from the study because of adverse side effects (diarrhoea, tremor and somnolence). There was no significant improvement in depression scores measured by Beck Depression Inventory, anxiety tested by the State-Trait Anxiety Inventory, exercise capacity examined by twelve-minute walk test, and physiological parameters were examined using spirometer for lung function tests.

Nortriptyline

Borson and colleagues, in a double-blind, placebo-controlled trial, examined [25] the efficacy of 12 weeks nortriptyline of in patients with COPD patients with major depression, confirmed by psychiatrists using the Structured Clinical Interview for DSM-III. Nortriptyline was started at 0.25 mg/kg of body weight and increased weekly up to 1 mg/kg. Thirty participants with COPD completed the study. The nortriptyline group showed greater improvements in depression, anxiety, respiratory symptoms and daily activities compared to the placebo group. However, there was no improvement in physiological outcomes in either group.

Protriptyline

Strom et al. [26] examined the efficacy of protriptyline, 10 mg/d for 12 weeks, in a double-blind randomised trial. Twenty-six participants with COPD and chronic hypoxaemia and depression, defined by the Hospital Anxiety Depression Scale, started the trial but only five completed it. Twelve participants in the protriptyline and six participants in the placebo group discontinued treatment due to adverse events, the most commonly reported of which were anticholinergic side effects, i.e. dryness in the mouth. There was no improvement in arterial blood gas tensions, spirometry values, and dyspnoea and quality of life scores in either group.

In summary, the efficacy of antidepressant drugs using both SSRIs and TCAs for treatment of depression in patients with COPD was inconclusive. Findings from the current literature are greatly limited by methodological weaknesses including low sample size, sample heterogeneity and variation in the screening and diagnostic tools used to measure and to monitor the treatment of depression [14]. In addition, which specific SSRIs or TCAs may be appropriate to treat depression in patients with COPD requires further investigation in larger randomised controlled trials since to date there have been no head-to-head studies of different antidepressants.

Barriers to Treatment of Depression in COPD

Treatment of depression in people with COPD can be a challenge. A recent national survey of general practitioners (GPs) in England reported that convincing COPD patients with comorbid depression to receive appropriate treatment was an arduous task [27]. Reasons for this include patient misapprehension of antidepressants, fear of the side effects of antidepressants, misconceptions that antidepressants are addictive and difficult to 'come-off', and stigma attached to depression and mental illness [27]. Furthermore, the lack of adequate provision of psychological services and long waiting times for psychological treatment represents another barrier to adequate management of depression in COPD [27, 28].

In contrast to conventional therapeutic approaches, the collaborative care model (CCM) has been shown to improve treatment adherence [29] and improve quality of life and reduce healthcare utilisation in patients with chronic diseases with major depression. The CCM is a behavioural management approach; which is administered by trained case managers, who work collaboratively with each patient to implement their individual treatment plan. Care managers will identify barriers to adherence specific to each patient and, through education and support, help promote adherence to antidepressants drug therapy. They will engage with the patient on a regular basis either face-to-face or by phone. In addition, the care manager will monitor the patient's condition regularly and if adverse events arise, will communicate with the patient's primary care physician or psychiatrist. To date, the efficacy of CCM for managing depression in COPD is unknown.

A recent systematic review [30] investigated complex interventions including education, exercise therapy life style interventions and cognitive behavioural therapy on the efficacy of treatment of depressive symptoms. Thirty independent comparisons from 29 randomised controlled trials (n = 2063) were included in the meta-analysis. Overall, psychological and/or lifestyle interventions were associated with small reductions in symptoms of depression (standardised mean difference −0.28, 95% confidence interval −0.41 to −0.14) and anxiety (standardised mean difference −0.23, 95% confidence interval −0.38 to −0.09). Multi-component exercise training was the only intervention subgroup associated with significant treatment effects for depression (standardised mean difference −0.47, 95% confidence interval −0.66 to −0.28) and for anxiety (standardised mean difference

−0.45, 95% confidence interval −0.71 to −0.18) [30]. However, the efficacy of these interventions on depression severe enough to meet criteria for major depression is unclear. This is partly due to some of the reviewed studies being uncontrolled and underpowered to show the magnitude and the efficacy of the intervention to ameliorate depression. Another systematic review and meta-regression analysis [31] that examined the efficacy of antidepressants for older adults with chronic diseases, including COPD, advocated that future research should focus more on the benefits of combining psychotherapy and antidepressant drug therapy to maximise efficacy in the treatment of major depression, rather than investigating single modality therapies by themselves.

Managing Depression in Patients with COPD

A number of studies have reported that both SSRIs and TCAs are associated with considerable side effects in patients with COPD and major depression. Hatcher and Arroll [32] provide helpful management plan of treating patients who experienced side effects commencing antidepressants such as diziness, sedation, dry mouth, sexual dysfunction, insomnia, suicidal thoughts, anxiety, hyponatraemia, serotonin syndrome, and discontinuation syndrome. This management approach will be helpful to treat COPD patients who experience side effects with antidepressants.

The Effect of Opioids and Benzodiazepine on Health Outcomes in Advanced Stage of COPD

The NICE recommends that opioids and benzodiazepine and major tranquilisers are appropriate in palliating symptoms in patients with advanced-stage COPD [33]. These agents should be used when patients with advanced stage of COPD with intolerable dyspnoea are unresponsive to other medical therapy. However, American Thoracic Society/European Respiratory Society guidelines warn against the use of benzodiazepines and recommend avoiding hypnotics, if possible, in patients with severe COPD [34]. Despite these warnings, benzodiazepines are widely used in older adults in patients with COPD [35]. Benzodiazepines are prescribed including treatment for insomnia, agitation, depression and anxiety, and refractory dyspnoea, which are common in advanced stage of COPD [11].

Dyspnoea

Excessive dyspnoea on exertion is a hallmark of advanced stage of COPD, and it is disabling and challenging to treat. Dyspnoea impairs quality of life, increases dependency on others for daily activities and decreases social interaction.

The prevalence of breathlessness with minimal exertion or at rest is as high as 90% in patients with advanced COPD compared with 60% in patients with chronic heart disease [36]. There are a number of options of treatment that are available to relief the distressing symptoms of breathlessness in patients with severe COPD including bronchodilators, long-term oxygen therapy (LTOT), pulmonary rehabilitation and use of opioids [33, 37]. Other forms of therapy to reduce the sensation of dyspnoea include the use of a fan direct cooler to the face, which showed some benefits in normal subjects [38], LTOT for hypoxemic patients [39], pursed-lip breathing, relaxation techniques and smoking cessation could be effective strategies for relief of dyspnoea. The judicious use of bronchodilator therapy in dyspnoeic patients is recommended. However, apart from optimising (active) medical treatment for patients with advanced COPD, opioids remain the most effective dyspnoea relieving medications and cough in end-of-life care [40, 41] as recommended by the Canadian Thoracic Society [41]. The American College of Chest Physicians consensus statement [42] affirms the use of opioids, but the dose should be titrated for individual patient with consideration of multiple factors (e.g. renal, hepatic, pulmonary function and past opioids use) for relief of dyspnoea. It is important to monitor patient's condition regularly for benefits and side effects and adjust accordingly any of the medication on an individual basis.

As there are fewer than handful studies, that investigated the benefits of Benzodiazepines and/or opioids in patients with advanced COPD, and largely in small sample size and uncontrolled, and short-term duration of intervention. Therefore, this review provides summary of these study findings including population-based studies as follows.

Benzodiazepine

A recent national prospective study in Sweden [43] examined the safety and effects of benzodiazepines and opioids in patients with severe respiratory diseases on rates of admission to hospital and mortality. All patients were using LTOT during the four-year follow-up. Over three quarter of the patients were admitted to hospital because of acute exacerbations. Fifty per cent of the patients died during the observation period. Benzodiazepine and opioids were not related to hospital admission. The use of benzodiazepines was associated with 21% increased mortality with a higher level of dose response trend. Opioids had a dose response rate with mortality: lower doses of opioids (≤ 30 mg oral morphine equivalents a day) were not associated with elevated mortality. In contrast, higher dose of opioids was associated with increased mortality by 21%. Their findings indicate that concurrent use of benzodiazepines and opioids in lower doses to treat severe dyspnoea in patients with COPD is not associated with increased hospital admissions or mortality. In this study, the most commonly used benzodiazepines were oxazepam (74%), diazepam (17%) and alprazolam (8%). In the study the weak opioids were tramadol (31%), codeine (19%), and dextropropoxyphene (15%) and strong opioids

were oxycodone (15%), morphine (11%) and fentanyl (5%). Benzodiazepines and higher dose opioids were associated with increased mortality. Lower dose of opioids are not associated with elevated mortality or hospital admissions in patients with COPD and might be safe to relieve symptom of dyspnoea in patients with respiratory diseases [43].

Vozoris et al. [44] investigated the use of benzodiazepine and the potential risk of adverse respiratory outcomes in patients with COPD. This seven-year retrospective population-based Canadian study comprised of 177,355 community-dwelling individuals with COPD who were aged 66 years and older. Of these, 50,358 (28.4%) were new benzodiazepine users. Their findings indicated that benzodiazepine users were at significantly higher risk for outpatient respiratory exacerbations (relative risk, 1.45, 95% Confidence interval 1.36–1.54) and emergency room visits for COPD or pneumonia (relative risk 1.92, 95% Confidence interval 1.69–2.18) compared to non-users [44]. Likewise, no significant differences between new users and non-users of benzodiazepines were observed in regard to intensive care admissions during hospitalisations for COPD or pneumonia. Thus, caution should be exercised when prescribing benzodiazepine in older patients with COPD and plan appropriate strategies, e.g. regular monitoring to reduce adverse respiratory outcomes.

A recent Cochrane review examined the efficacy of benzodiazepine [45] to relieve the symptoms of breathlessness including advanced stages of cancer, COPD, CHF, motor neuron disease (MND) and idiopathic pulmonary fibrosis (IPF). The review identified seven studies that included 200 subjects with advanced cancer and COPD. Analyses of these seven studies did not identify the beneficial effect of benzodiazepines for the relief of breathlessness in patients with advanced cancer or COPD. The authors performed sensitivity analyses to show differences in relation to type of benzodiazepine, dose, route and frequency of delivery, duration of treatment or type of control [45]. There were no significant differences in any of the physiological parameters. Benzodiazepines caused more drowsiness as an adverse effect compared to placebo, but less compared to morphine. The authors suggest benzodiazepines should be considered as the last resort [45], if there was no improvement using opioids and other non-pharmacological treatments to control breathlessness.

Temazepam

A double-blind, placebo-controlled trial, cross-over study [46] examined the efficacy of 10 mg temazepam or placebo once daily for one week in [n = 14 stable COPD patients] with chronic insomnia. The washout period was one week. Findings indicate that one-week usage of temazepam does not influence circadian respiratory function, dyspnoea and sleepiness in patients with severe normocapnic COPD with insomnia. However, it improves total sleep time and subjective sleep latency. This study was a preliminary explorative study. Therefore, further studies

are required to examine the clinical efficacy of temazepam in larger sample size and with longer duration time.

Opioids

Morphine with Clonazepam

In a single site, open-label phase II study, Allcroft and colleagues [47] examined the additional benefits of regular clonazepam 0.5 mg nocte orally to Kapanol (R) 10 mg (sustained-release morphine sulphate) orally mane together with docusate/sennosides in people with modified Medical Research Council Scale ≥ 2 over 4 days. The primary outcome was the intensity of breathlessness on day four. Patients were allowed to extend for another 10 days if they achieved >15% reduction over their own baseline breathlessness intensity. Eleven COPD patients (8 = male) were recruited, and (n = 10) completed day four duration of intervention. The median age was 76 years. One person withdrew because of unsteadiness on day four. Five participants reached the 15% reduction in the level of breathlessness, but only three went on to the extension study, and all patients completed the study without toxicity [46]. The findings indicate it was safe and feasible and there appears to be as a whole group who derive benefits comparable to titrated opioids. However, further studies are required to examine the efficacy of clonazepam in larger randomised controlled trial.

Morphine

Abernety et al. [48] examined the efficacy of oral morphine in relieving the sensation of breathlessness measured by patients with COPD with optimum medical treatment was randomised to four days of 20 mg oral morphine with sustained release followed by four days of identically formulated placebo, or vice versa. Forty-eight participants who had not previously been treated with opioids (mean age 76, SD 5) years started the trial. Out of these, 38 participants completed the trial, three withdrew because of definite and two because of possible side effects of morphine (nausea, vomiting and sedation). Their findings indicate that when patients were receiving morphine their dyspnoea scores were significantly reduced and had better sleep compared when they were not. However, participants reported distressing constipation while they were receiving morphine. Thus, sustained release, oral morphine at low dosage provides significant symptomatic improvement in refractory dyspnoea in patients with COPD in the community setting. However, the long-term benefit of morphine requires further testing.

Currow and co-workers [49] examined the minimum effective once-daily dose of sustained-release morphine, and whether net clinical benefits are sustained safely in patients with respiratory diseases with refractory dyspnoea (breathlessness that

cannot be relieved with regular medication) including COPD patients with the 3-month follow-up. This dose increment study started with 10 mg daily of sustained-release morphine and increased in non-responders by 10 mg daily each week to a maximum of 30 mg daily. Patients were withdrawn from the study when they experience intolerable side effects or no response to the maximum dose to reduce breathlessness. Eighty-three patients (53 males, mean age 75 years, 54% with chronic obstructive pulmonary disease) were recruited to the study. Over three-fifths of the patients derived $\geq 10\%$ benefit (on average 35% improvement over baseline), with the dose of 10 mg/24 h in reducing dyspnoea. These benefits were sustained at three months by 28 (33%) of the patients. In addition, statistical significant improvement was observed in the level of dyspnoea at $p < 0.0001$. However, a significant proportion of patients developed constipation during the study period, despite receiving laxatives. It demonstrates ten milligrams of sustained-release oral morphine once daily is safe and effective for those patients who respond.

Challenges in the Use of Opioids

A small pilot study [50] investigated the views of the healthcare professionals [$n = 18$] including respiratory therapists and family physicians in the primary care settings in the use of opioids for the treatment of refractory dyspnoea in patients with advanced COPD. They have reported the value of opioids to relieve the symptoms of dyspnoea in advanced stage of the disease. However, family physicians have reported their discomfort (uneasiness) of prescribing opioids routinely for the treatment of dyspnoea. Furthermore, they have identified insufficient knowledge of the participants, lack of education and guidelines when to prescribe opioids and fear of censure. This underscores the importance of training and developing appropriate educational materials for healthcare professionals including family physicians in the use of opioids and the value of palliation for patients with advanced stage of COPD to treat distressing dyspnoea-related symptoms.

A recent retrospective review of four international studies of 213 individuals of pooled analysis data [51] examined factors that predict better opioids response in the treatment of refractory dyspnoea in patients with severe chronic respiratory diseases. Their findings indicate that higher baseline breathlessness intensity scores were strongly predicted by absolute and relative response ($p < 0.001$). In addition, younger age patients with worse breathlessness are more likely to derive greater benefit in the treatment of opioids. Although opioids have a role in the treatment of refractory dyspnoea, it requires careful monitoring of individual patient to maximise benefits. This is crucial, as the therapeutic index may be narrower for older patients with less to gain. 'Likewise, older people are at particular risk of excessive fatigue and decrease in ADL, drug–drug interaction and drug–host-related adverse events' [50]. This review highlights the paucity of evidence, the therapeutic dosage and duration of treatment of opioids to treat patients with respiratory diseases with refractory dyspnoea and pain. Thus, well-controlled prospective studies are needed.

A retrospective study from the administrative data [52] from the Veterans Affairs (VA) patients with posttraumatic disorder (PTSD) examined the safety of combinations of benzodiazepine and opioids and selective serotonin reuptake inhibitors (SSRIs) or serotonin/norepinephrine reuptake inhibitors (SNRIs). The study compared the 2-year incidence of adverse events among VA patients with PTSD [n = 5236] exposed to combination groups. They have reported that either SSRIs or SNRIs in combination with benzodiazepine and opioids were associated with increased hospitalisations for mental health-related problems and increased for medicine/surgery hospitalizations and emergency department visits and harmful events (e.g. injuries and death) compared to those prescribed SSRIs/SNRIs only. Therefore, regular monitoring and close follow-up of patients are required especially to those patients prescribed combined medications in order to reduce the adverse events. Furthermore, the efficacy and applicability of concurrently prescribing of these combined drugs has not been examined to treat intolerable dyspnoea or pain in patients with advanced stage of COPD. Therefore, well-controlled trials are needed.

Table 11.1 Clinical tips for the use of antidepressants and anxiolytics therapy for patients with respiratory diseases

General points
• The evidence available for the use of antidepressants drug therapy to treat comorbid depression in patients with COPD is inconclusive [53, 54]. In the absence of clear evidence of benefits, it is important for clinicians to monitor COPD patients using a validated depression rating scale regularly and following any patient who has been prescribed antidepressants to determine response to therapy and the emergence of the prescription of antidepressants for any adverse events.
• When prescribing antidepressants, the principle of 'start low and go slow' should be followed provided there is an attempt to but try not reach a therapeutic dose in patients with adequate tolerance.
• Prior to commencing antidepressant drug treatment, COPD patients should be informed of potential side effects. It is important to emphasise that most of side effects are transient and to ensure that clinician backup is easily available make yourself available in case side effects develop.
Specific medication points
• Depressed COPD patients who are poorly tolerating or failing to respond antidepressants should be referred to a psychiatrist for detailed assessment.
• In older people, it has been reported over the third of the patients [49] on SSRIs and tramadol or oxycodone exhibit drug interactions. Thus, older patients who are treated with combined drugs require close monitoring and adjust the therapeutic doses accordingly in relation to patients' symptoms in order to reduce potential side effects. Opioids in lower doses (<30 mg oral morphine equivalent per day) are not associated with increased hospital admission or deaths in patients receiving long-term oxygen therapy for COPD.
• Benzodiazepines and opioids in higher doses might increase mortality in patients with chronic respiratory diseases.
• Lower-dose opioids might be safe for reducing symptoms of dyspnoea in patients with respiratory disease.
Safety data from clinical practice for benzodiazepines and opioids in patients with severe COPD are lacking.

Conclusion

The available evidence suggests that the efficacy of antidepressants drug therapy in people with COPD and major depression is inconclusive. Therefore, appropriately powered prospective randomised controlled trials are needed. General guidance and specific medical points are provided in how to use antidepressants and anxiolytics in patients with COPD as outlined in Table 11.1.

Lower doses of opioids are beneficial in ameliorating dyspnoea in patients with COPD without series adverse events. However, only a few studies have been conducted to address this question and they are all small in sample size. Thus, again, prospective randomised controlled trials with larger sample sizes are required. Additionally, the safety of benzodiazepines for use in patients with severe COPD requires further investigation.

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Chapter 12
Palliative and End-of-Life Issues in Patients with Advanced Respiratory Diseases

Glencora Sharfman, MD and Ursula K. Braun, MD, MPH

Introduction

Dyspnea, cough, anorexia, fatigue, anxiety, and depression are symptoms commonly experienced by patients with advanced diseases of the respiratory system. Though by varying mechanisms, diseases affecting the respiratory system including chronic obstructive pulmonary disease (COPD), interstitial lung diseases, primary lung malignancies, and other cancers with metastases to the lungs may present with these clinical manifestation that may worsen with progression of disease. Comorbid conditions, in particular congestive heart failure, also can contribute to worsening of dyspnea.

The most common symptom in all respiratory diseases is dyspnea. The term dyspnea originates from the Greek roots *dys*, meaning painful or difficult and *pneuma*, meaning breath to describe the symptom of breathlessness or difficulty breathing in healthy individuals and people with diseases affecting the respiratory system [1, 2]. Treating persistent dyspnea becomes increasingly important as activities of daily living become impaired, and progression of this symptom is a better indicator of progression of disease than formal testing including lung function studies. This is underscored by a study on dyspnea in COPD showing dyspnea to be a better predictor of health-related quality of life (HRQOL) and mortality than severity of airflow limitation [3].

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Pathophysiology of Dyspnea

The sensation of dyspnea can be separated into two components comprised of "air hunger," or the urge to breathe, and the sense of excessive effort of breathing [4]. Due to the nature of dyspnea as a visceral sensation rather than a localized, peripheral sensation, the exact mechanisms of dyspnea are incompletely understood. Activation of limbic, paralimbic, and cerebellar structures has been identified on MRI during dyspnea [5]. Activation of these primitive regions of the cerebral cortex has also been demonstrated with pain, hunger, and thirst, consistent with the idea that these structures play a role during any urgent homeostatic imbalance to counteract a threat to survival.

The pathophysiology is theorized to result from a disassociation between central respiratory motor activity and afferent information from receptors in the lungs, airways, and chest wall, which in turn stimulate respiratory-related neurons in the brainstem. Heightened ventilatory demand may be induced by hypoxia, hypercapnia, metabolic acidosis, and exercise [6]. Increases in ventilation are required to compensate for the enlarged dead space from pulmonary disease; however, patients with advanced disease are often deconditioned due to prolonged inactivity. Deconditioning is associated with higher lactate levels, which in turn increases ventilation with exercise and worsens the sensation of dyspnea [7]. This cycle of deconditioning leading to further dyspnea is seen in functional decline with normal aging as well as advanced pulmonary disease.

Measurement of dyspnea is subjective and can be rated on a scale from 1 to 10, similar to a pain rating scale. A numerical rating scale for dyspnea (NRS-D) and a visual analog scale for dyspnea (VAS-D) have been developed and are commonly used. The Modified Borg Scale has descriptors associated with each of the numbers [8]. Alternatively, a scale such as the Medical Research Council (MRC) Breathlessness Scale might be used—it suggests five different grades of dyspnea based on the circumstances in which it arises [9]. In palliative patients with lung cancer, the English version of the cancer dyspnea scale has been found useful [10]. Dyspnea is also routinely assessed during a general palliative care symptom assessment using the Edmonton Symptom Assessment Scale [11].

Management of Dyspnea

Supplemental oxygen is routinely offered to dying patients with dyspnea, but its value in relieving symptoms in non-hypoxemic patients has been questioned [12]. The goal of oxygen therapy is to decrease hypoxic drive mediated by peripheral chemoreceptors in the carotid body in hypoxemic patients. Reducing chemoreceptor activation will cause decreased ventilation. Oxygen may also blunt pulmonary artery pressure rise associated with strenuous activity. While benefit of supplemental oxygen to improve exercise tolerance has been shown for mildly

hypoxemic COPD patients, studies of COPD patients without resting hypoxemia showed no significant improvement in exercise tolerance or dyspnea with supplemental oxygen [10, 13, 14]. In patients with advanced cancer in a hospice setting, supplemental oxygen was found to be equally effective as room air in reducing dyspnea, with improvement in dyspnea unrelated to a subject's initial level of hypoxia [13, 15, 16]. It is possible that the perception of airflow alone led to subjective improvement in dyspnea [17]. This might also be accomplished with the use of fans; however, few high quality studies are available [18]. Supplemental oxygen therapy was found to have no effect in palliative patients with normal blood oxygen saturations in a double-blind, randomized controlled trial [12]. However, the clinical practice of offering oxygen to dying patients despite lack of evidence is commonplace and may be due to practical issues: in most hospice settings pulse oximetry is not used and thus differentiating which patients are hypoxic and might benefit from oxygen therapy from those who are not is not possible. If supplemental oxygen is administered, via nasal cannula is preferred over facemasks which can interfere with eating and talking. Noninvasive positive pressure ventilator support (NPPV) can treat dyspnea in COPD patients but it is often poorly tolerated or perceived as uncomfortable, and occasionally anxiety-provoking [19–23]. Physical inactivity has also been demonstrated to increase perception of dyspnea in COPD [12]. While patients with advanced pulmonary disease will likely have limited exercise capacity, exercise programs tailored to one's capabilities may offer some benefit in alleviating dyspnea [15].

Other non-pharmacologic interventions for dyspnea in advanced malignant and non-malignant diseases with at least some evidence of effectiveness are chest wall vibration, neuro-electric muscle stimulation, and breathing training [24]. Chest wall vibration (CWV) is thought to stimulate afferent impulses from intercostal muscles on cortical centers, reflex suppression of brainstem respiratory output, and decrease the sense of respiratory effort. Tidal volume has been shown to significantly increase following therapy [23]. In neuromuscular electrical stimulation (NMES) electric impulses are used to elicit muscle contraction. This therapy has been used in severe COPD patients to increase muscular oxidative capacities to help facilitate rehabilitation in patients with incapacitating dyspnea which has shown to improve muscle strength and endurance, exercise tolerance, and breathlessness during activities of daily living in small studies [26]. Breathing training may include techniques such as pursed-lips breathing (PLB) which attempts to prolong active expiration through constricted lips. Compared with spontaneous breathing, PLB has shown to decrease the respiratory rate and dyspnea as well as improve tidal volume and oxygenation at rest [27]. There is low evidence for benefit of acupuncture and acupressure, and not enough date available to evaluate the benefit of relaxation techniques, fans, counseling and support, or distractive auditory stimuli [28]. Though further studies are needed to validate these non-pharmacologic treatment options, patients should be evaluated on an individual basis for treatment in the setting of progressive symptoms despite pharmacologic agents.

Pharmacologic Therapy for Dyspnea

The two groups of medications used to treat dyspnea are opiates and anxiolytics. Opioids have long been established as an effective treatment in relieving dyspnea in COPD patients, patients with advanced cancer, and terminally ill patients [2, 29–31]. Opiates have been shown to decrease ventilation at rest and during submaximal levels of exercise, modulate dyspnea in acute bronchoconstriction, and may blunt or suppress perception of respiratory sensation [32]. Nearly all routes of administration are effective; only nebulized morphine has been shown to have no effect on dyspnea in several studies [33, 34]. The most common side effects are seen on initiation of therapy and are dose dependent, with the most frequent side effects observed including constipation, nausea, and somnolence. Appropriately titrated, opiates have been shown to be safe and effective for dyspnea due to multiple etiologies [1, 2, 30, 35, 36]. Opioid-naïve patients will usually respond to low doses of oral or parenteral morphine; higher doses are necessary for those on chronic opioids and must be individually titrated. Acute severe dyspnea should be rapidly treated with parenteral opioids, and some patients may require continuous infusion of a basal rate. Some clinicians hesitate to use opiates for dyspnea (or pain) due to unfounded concerns about respiratory depression, a quite rare event that is preceded by drowsiness; thus it is always advisable when ordering opioids to specify "hold for sedation/difficulty arousing patient." Opiates can be titrated to effect, e.g., goal is to reduce a dyspnea score to 3 or below. Dying patients who no longer can self-report dyspnea can be assessed by looking for distress like gasping or grimacing and opioid titration can follow the respiratory rate, e.g., with a goal to reduce respiratory rate to 20s or close to normal.

Dyspnea is frequently associated with or exacerbated by anxiety. Anxiolytics have been proposed to relieve dyspnea by depressing hypoxic or hypercapnic ventilatory responses as well as treating underlying anxiety that may contribute to a sensation of dyspnea. Benzodiazepines have been most frequently studied anxiolytics for use in dyspnea with no benefit found in patients with dyspnea due to advanced cancer or COPD [37]. However, one study with buspirone, an anxiolytic with no sedative effects, found significant improvement in depression and anxiety, as well as improved exercise tolerance and dyspnea following treatment [38]. Further studies are needed to assess the benefit of anxiolytics in treatment of dyspnea in advanced lung diseases.

"Death rattle"

Imminently dying patients are unable to clear secretions and have impaired cough and gag reflexes. Saliva accumulated in the posterior oropharynx and secretions in the tracheobronchial tree can lead to 'noisy breathing' and sounds resembling choking that can be distressing to families. This 'death rattle' and should be

thoroughly explained to families; it does not always warrant treatment as there is no evidence that it is distressing to the patient. Repositioning the patient can lead to postural drainage and improve symptoms; anticholinergic medications like atropine, scopolamine, or glycopyrrolate are often used if the family finds it too distressing [39, 40].

Cough

Another common and very bothersome symptom in advanced airway diseases is cough.

A cough is defined as a deep inspiration followed by a strong expiration against a closed glottis. While identified as a prevalent symptom in COPD, cough has not been shown to have the same association with the degree of airway obstruction as progressive dyspnea. Cough is independent of severity of disease due to a heightened cough reflex sensitivity in both COPD and asthma, by which the sensitivity of the lining of the airways results in medulla-mediated afferent impulses of the vagus nerve resulting in cough. Cough, anorexia, fatigue, and anxiety are all frequently reported symptoms of patients with advanced airway diseases, though may have a smaller relative contribution to disability.

Pathophysiology of Cough

Cough is a complex physiological reflex initiated by activation of vagal afferent nerves innervating the airways and lungs [7]. Afferent pathways from receptors in and under the epithelium of the airways are rapidly adapting and can be stimulated directly by tussive agents which can be either chemical or mechanical irritants [41]. Though cough is a defense mechanism, modulation of the cough reflex pathway in disease states can lead to an augmented cough response, as seen in COPD and asthma [42, 43]. Disease states specifically cause an increase in sensitivity of rapidly adapting irritant receptors (RARs) in the tracheobronchial tree and C-fiber receptors located in laryngeal, bronchial, and alveolar walls. RARs are normally silent, but when activated cause rapidly adapting discharges with an irregular pattern that are conducted in vagal nerve fibers, provoking cough. RAR stimulants include cigarette smoke, ammonia, ether vapor, acid and alkaline solutions, hypotonic and hypertonic saline, and mechanical stimulation by catheter, mucus, or dust. RAR activity is enhanced by pulmonary congestion, atelectasis, bronchoconstriction, and decreases in lung compliance [2, 31]. C-fiber receptors have thin nonmyelinated vagal afferent fibers and are activated by the same stimuli as RARs. However, their activation does not induce cough, but instead release tachykinins such as substance P, which in turn stimulate RARs to cause cough.

Pharmacologic Therapy for Cough

In severe COPD and other advanced pulmonary diseases in a palliative setting, opiates have been established to be effective therapy. Opiates are thought to inhibit cough by affecting primarily the μ-opioid receptor in the central nervous system. Morphine, codeine, and dihydrocodeine may be considered goal standard narcotic antitussive agents [22, 23]. Studies in palliative cancer patients have validated the efficacy and safety of hydrocodone as treatment for cough, though the same rate of efficacy has not been consistently shown in patients with COPD [44, 45].

Mucolytics have not been found to consistently ameliorate cough. Cough suppressant therapy is found most effective for short-term reduction in coughing only. These drugs are non-specific, intended to suppress cough regardless of etiology. These drugs target multiple mechanisms of cough by affecting mucociliary factors (i.e., guafenasin), the afferent limb of the cough reflex (dextromethorphan), the central mechanism for cough (opioids), the efferent limb of the cough reflex (baclofen), and skeletal muscles (succinylcholine, propofol) [46].

Anorexia, Cachexia, and Muscle Wasting

In addition to pulmonary manifestations, patients with advanced pulmonary diseases develop systemic complications including anorexia, weight loss, cachexia, and muscle wasting. Pulmonary cachexia is recognized feature of COPD, with the exact mechanism in this disease poorly understood. Potential factors include oxidative stress, inflammation, and muscle wasting. Muscle wasting has been demonstrated in COPD due to alterations in protein synthesis [47, 48]. Whole-body protein synthesis is depressed, accompanied by an overall fall in whole-body protein turnover. However, skeletal muscle dysfunction, independent of lung function, has been shown to contribute significantly to decreased exercise capacity and a poor quality of life [49]. Limb and skeletal muscle dysfunction is exacerbated by low-grade systemic inflammatory processes, malnutrition, corticosteroids, hypoxemia, oxidative stress, protein degradation, and changes in vascular density. Muscular remodeling has been observed in COPD by means of fiber-type redistribution [50]. The proportion of type-I fibers was found to be markedly lower in COPD, with a higher proportion of type-II fibers, which have a lower oxidative capacity. In further studies, reduced oxidative capacity has grossly been demonstrated in patients with moderate to severe COPD [42, 43]. Additionally the capillary to fiber ratio in muscles from subjects with COPD was found to be reduced [51]. While other alterations in the mechanisms of protein degradation and synthesis are still being investigated, it is evident that skeletal muscle dysfunction separate from muscle wasting contributes significantly to the progression of symptoms and decline in quality of life in those with COPD.

Anxiety and Depression

Patients with advanced illness often experience anxiety and depression, and up to 50% of patients with incurable conditions carry psychiatric diagnoses [52]. While periodic feelings of depression or anxiety are normal, high levels of persistent anxiety or depression are not an inevitable part of serious illness or of the dying process [53]. The Canadian National Palliative Care Survey found that 13% of palliative care patients fulfilled criteria for major depression, rising to 44% when patients with milder depressive symptoms, dysthymia, and other depressive disorders were included [54].

Differentiating depressive disorders from an appropriate grief reaction in the setting of a terminal illness may be difficult, and under-detection and under-treatment of the psychological and psychiatric morbidity developed in terminally ill patients is common [55–57]. Normal sadness and grief at the end of life are proportionate to the patient's loss and degree of disability, with the capacity for pleasure in some aspects of life retained. Patients with clinical depression will experience disproportionate dysphoria, anger, or social withdrawal. While both groups of patients may think about death, patients with clinical depression may become preoccupied with death and lose touch with past values.

A Cochrane meta-analysis ($N = 292$ patients in the psychotherapy arms and $N = 225$ patients in the control arms) on psychotherapy for depression among incurable cancer patients found that psychotherapy was associated with a significant decrease in depression scores [50]. The quality of all of these trials was poor to fair. Additionally, none of the patients had clinically diagnosed depression, and efficacy was evaluated by change (decrease) in depressive symptom scores [55].

Anxiety disorders are prevalent in the general population, and are likely aggravated at the end of life. Factors contributing to heightened anxiety at the end of life include situational causes, drugs (corticosteroids, benzodiazepines, opioids, psychostimulants), uncontrolled pain, dyspnea, insomnia, or other organic etiologies. Anxiety symptoms may also be triggered by medical transitions such as recurrence or diagnosis of serious illness, treatment side effect or failure, or fear of impending death.

Anxiety disorders, especially generalized anxiety disorder (GAD) and panic attacks have been shown to occur at a higher rate in COPD patients, with the prevalence of panic disorder up to ten times that in the general population [58]. Anxiety has a significant impact on the quality of life in COPD patients. One study showed COPD patients with panic disorder had greater perceived dyspnea than those without panic disorder [59]. As anxiety is shown to heighten the sensation of dyspnea without relation to respiratory variables, this highlights the importance of addressing psychological factors in symptom management.

The treatment of both anxiety and depression frequently involves a combination of supportive and existential therapy, structured cognitive behavioral therapy, and pharmacologic treatments [57–62]. An accurate and timely diagnosis of depression is critical, as depression may lead to a lower functional status and hinder adherence

with treatments. Depression has also been shown to be associated with an increased risk of mortality among cancer patients [63]. This may be related to a reduced ability to cope with either physical or psychological issues that arise as illness progresses, resulting in increased dysfunction and suffering. Treatment should begin with identifying and correcting any physical causes if possible. This may include treating reversible cause of fatigue or withdrawing offending medications. Pharmacologic agents are the mainstay of treatment, including antidepressants, psychostimulants, and mood stabilizers. A medication should be chosen on the basis of desired effects, possible interactions, and side effects. For example, a sedating antidepressant can be used as a sleep aid. Psychotherapy should be offered to all terminally ill patients suffering from depression. The choice of therapy is determined by the goals of the patient, the ability of the patient to engage in therapy, the awareness of the emotions present, and the ability to communicate those thoughts and feelings. Therapy may help reduce fear and distress, maintain personal sense of dignity, maintain relationships, and attempt to reach realistic goals.

Pharmacologic Management of Anxiety

The goal of treating anxiety is to reduce anxiety and allow for a normal coping response, not to render a person 100% anxiety free. Benzodiazepines are the mainstay of treatment for treatment of anxiety in a palliative setting and to relieve episodes of brief anxiety. For anxiety due to events occurring over a discrete time period, short-acting benzodiazepines such as alprazolam or lorazepam may be used on an as needed basis [64]. A patient who is anxious and confused may benefit from a less sedating agent such as haloperidol as needed [64]. For long-term anxiety in patients with a prognosis of several months or longer, SSRIs are a good treatment option [63]. However, as this group of medications will take 2–6 weeks for onset of action, a benzodiazepine may be used concurrently until the SSRI becomes effective, at which point it may then be withdrawn.

Interdisciplinary Approach

An interdisciplinary approach is crucial to the delivery of care for patients with end-stage illnesses. The need for professionals to collaborate has been an emerging issue in healthcare. The term interdisciplinary is used to describe a team of members from multiple disciplines who work collaboratively to provide care. The collaboration and interdependence in an interdisciplinary approach is becoming recognized as an optimal approach to care and is a cornerstone for hospice and palliative medicine [66]. A palliative care team will often comprise of chaplains, nurses, home health aides, nutritionists, psychiatrists, psychologists, social workers,

and physicians. This network available to patients not only addresses symptom management, but also offers social and spiritual support as well as mental health services as a comprehensive service. Patients receiving palliative care services report an increased quality of life [47, 48]. In addition to improvements in quality of life and mood, recent evidence also shows that early palliative care at the end of life may prolong survival in end-stage lung cancer [67]. Due to the growing evidence of the numerous benefits of the comprehensive care offered in hospice and palliative medicine, an early palliative care referral should be offered to all patients with advanced lung diseases to add additional layers of support in conjunction with ongoing medical therapies.

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