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Cognitive behavioural therapy (CBT) for patients with

chronic lung disease and psychological comorbidities

undergoing pulmonary rehabilitation

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Abstract

Background: Anxiety and depression are psychological conditions that are highly prevalent among patients with chronic lung disease. These conditions are associated with increased morbidity and, in certain groups, increased mortality. Cognitive behaviour therapy (CBT) has shown potential as a treatment of anxiety and depression among patients with COPD, asthma and bronchiectasis. Pulmonary rehabilitation has the strongest evidence regarding its benefit in these patients, mainly through improved physical capacity and education. Consequently, the combination of both treatments (CBT and pulmonary rehabilitation) is promising, with potentially enhanced therapeutic benefits. The primary aim of this thesis was to determine the impact of cognitive behavioural therapy (CBT) as a treatment for patients with chronic lung disease and psychological comorbidities undergoing pulmonary rehabilitation. The study also assessed risk factors for the presence of anxiety and depression in patients attending pulmonary rehabilitation, the effect of CBT on quality of life and, through a subgroup analysis, the impact of mild cognitive impairment on CBT.

Methods: A parallel group, randomised controlled trial (RCT) was conducted, with longitudinal follow-up of 12 months. Participants were screened from the pulmonary rehabilitation program at The Prince Charles Hospital and recruited if they had Geriatric Depression Scale (GDS) ≥4/15 or Geriatric Anxiety Inventory (GAI) ≥3/20, suggestive of depression or anxiety, respectively. In addition to pulmonary rehabilitation, the Intervention group received CBT comprised by two face-to-face sessions and 4 phone sessions, while the Control group received usual care. The main outcome measures were GDS and GAI; secondary outcomes were St. Georges Respiratory Questionnaire (SGRQ), pulmonary rehabilitation attendance and 6 minute walk test (6MWT).

Results: The majority of patients attending pulmonary rehabilitation had COPD (58.5%), with the remainder having asthma (19.7%), interstitial lung disease (ILD) (9%) and bronchiectasis (12.4%). Of the patients screened, 25 (13%) had only symptoms of anxiety, 33 (17%) of only depression and 62 (32%) had symptoms of both anxiety and depression. Anxiety and depression were strongly correlated with SGRQ (p<0.01) and pulmonary rehabilitation program attendance. GDS scores were also correlated with 6MWT (p<0.01), past smoking (p<0.01), body-mass index (p<0.01),

and body-mass index, airflow obstruction, dyspnea, and exercise capacity index (BODE) scores (p<0.01); while GAI was not correlated with other parameters.

65 patients were randomised to the study (24 in the Intervention group, 41 in the Control group). Of the 24 patients in the Intervention group, 10 (42%) failed to attend pulmonary rehabilitation or withdrew from the study. In the Intervention group, GDS significantly improved, compared to baseline, at the end of rehabilitation (mean difference -3.1, 95% CI -4.39 to -1.7; P<0.01), 3 months follow-up (mean difference -1.46, 95% CI -4.17 to -0.75; P<0.01) and 12 months follow-up (mean difference -1.6, 95% CI -(-3.29 to -0.03; P=0.04). The Control group showed an improvement in GDS, compared to baseline, by the end of pulmonary rehabilitation (mean difference -1.34 95%, CI -2.4 to -0.27; p=0.01) but there was no statistically significant difference at 3 months (p=0.22) or 12 months (p=0.25) follow-up. There was a no statistically significant difference in GDS between Intervention and Control groups at by the end of rehabilitation (p=0.053), 3 months (p=0.29) and 12 months (p=0.2) follow-up. There was a significant improvement in GAI by the end of rehabilitation in the Intervention group (mean difference -2.6, 95% CI -4.69 to -0.57; P=0.01) and the Control group (mean difference -2.6, 95% CI -4.16 to -1.14; P<0.01), and no significant difference between groups (P=0.9). At 3 months there was no significant improvement in GAI in the Intervention group (P=0.07) or the Control group (P=0.14), which continued at 12 months follow-up for both the Intervention and Control groups (P=0.66) and (P=0.24), respectively. There was no statistically significant difference in GAI between groups by the end of rehabilitation (p=0.98), 3 months (p=0.59) and 12 months (p=0.74) follow-up.

There was no significant improvement in SGRQ, by the end of rehabilitation, 3 months and 12 months follow-up in each of the groups, and no significant difference between the Intervention and Control groups. There was no significant improvement in 6MWT in the Intervention and Control groups by the end of rehabilitation. There was a significant increase in attended pulmonary rehabilitation sessions in the Intervention group, compared to the Control group (mean difference 1.59; 95% CI 0.11 to 3.07; p=0.03).

Conclusion:

In this RCT of patients with chronic lung diseases attending pulmonary rehabilitation, there was no evidence found for improved symptoms of anxiety or depression or health-related quality of life with the addition of cognitive behavioural therapy given in a mixed face-to-face and telephone format, compared to usual care. The addition of CBT to pulmonary rehabilitation in patients with chronic lung disease was associated with a statistically significant ongoing improvement of symptoms of depression up to 12 months, however this was not significantly more than the Control group. CBT completion was associated with better pulmonary rehabilitation attendance; however, CBT treated patients had a high withdrawal rate, which may limit its clinical applicability. Slower than anticipated recruitment, leading to a smaller than planned sample size, and a high dropout rate in the group allocated to CBT may have limited the effectiveness of the behavioural intervention approach in this study. The improvement of depression scores after pulmonary rehabilitation could be better assessed in future larger studies, using treatments that target panic symptoms for patients with anxiety and use additional strategies to improve acceptance and adherence to psychological interventions by respiratory patients. In conclusion, this current study could not demonstrate evidence for the usefulness of CBT for patients with chronic lung disease and psychological comorbidities.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, financial support and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my higher degree by research candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications during candidature

Peer-reviewed paper

- Pumar MI, Gray CR, Walsh JR, Yang IA, Rolls TA, Ward DL. Anxiety and depression-Important psychological comorbidities of COPD. J Thorac Dis. 2014;6(11):1615-31.
- Pumar MI, Roll M, Fung P, Rolls TA, Walsh JR, Bowman RV, et al. Cognitive behavioural therapy (CBT) for patients with chronic lung disease and psychological comorbidities undergoing pulmonary rehabilitation. Journal of Thoracic Disease. 2019:S2238-S53.

Contributions by others to the thesis

- Tricia Rolls (Director of Psychology Department at The Prince Charles Hospital)
- Wrote the manualized cognitive behavioural therapy used during this project
- Supervisor of psychology interns implementing the therapy to patients
- Pamela Fung – Research Nurse (University of Queensland Thoracic Department at The Prince Charles Hospital)
- Patient screening and enrolment (May 2015 to December 2018)
- Follow-up calls and data collection
- Mark Roll – Senior physiotherapist (Pulmonary rehabilitation program at The Prince Charles Hospital)
- Patient enrolment
- Data collection

Statement of parts of the thesis submitted to qualify for the award of another degree

No works submitted towards another degree have been included in this thesis.

Research Involving Human or Animal Subjects

Human participants were involved in the study.

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Dedication

I dedicate this work to my wife and children.

Carlisa your support and faith has made this possible.

Estella and Raphael, for the joy you provide is the counterbalance for any long day.

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List of abbreviations

AIR	Anxiety Inventory for Respiratory Disease
BASDEC	Brief Assessment Schedule Depression Cards
BDI-II	Beck Depression inventory II
BMI	Body mass index
BODE	Body-mass index, airflow Obstruction, Dyspnoea, and Exercise
CBT	Cognitive behavioural therapy
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GAI	Geriatric Anxiety Inventory
GDS	Geriatric Depression Scale
GINA	Global Initiative for asthma
GMS	Geriatric Mental State Schedule
HADS	Hospital Anxiety and Depression Scale
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
NICE	National Institute for Health and Care Excellence
MAOIs	Monoamine oxidase inhibitors

MINI	Mini International Neuropsychiatric Interview
MCID	Minimal clinically important difference
MMSE	Mini Mental State Examination
mMRC	Modified Medical Research Council dyspnoea scale
MoCA	Montreal Cognitive Assessment
MPI	Minimal Psychological Intervention
PAH	Pulmonary arterial hypertension
RIMAs	Reversible inhibitors of monoamine oxidase A
SGRQ	St. Georges Respiratory Questionnaire
SNRIs	Serotonin and noradrenaline reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
sTNFR-1	soluble tumour necrosis factor receptor-1
TCAs	Tricyclic antidepressants
TNF-α	Tumour necrosis factor alpha
6MWT	6-minute walk test

INTRODUCTION

Introduction is an updated version of Pumar et al. (1).

Anxiety and depression are common comorbidities among patients with chronic lung disease. The presence of psychological comorbidities among chronic obstructive pulmonary disease (COPD) is high, with prevalence ranging from 10% to 57% (2-4) for depression, and from 7% to 50% (2, 5, 6) for anxiety. The impact of anxiety or depression in COPD patients is well documented and has been shown to be associated with increased mortality (7-9), exacerbation rates, length of hospital stay (10-15), and decreased quality of life and functional status (16-18). Although the prevalence and impact of psychological comorbidities have been documented more extensively for COPD, the limited studies regarding other conditions have shown that prevalence is also higher than the average population. For asthma, estimates for major depression among persons with asthma varied from 2% to 26% across the surveys, with prevalence generally between 5–10% (19). For idiopathic pulmonary fibrosis (IPF), pulmonary arterial hypertension (PAH) and bronchiectasis, the prevalence of depression or anxiety have been observed to be in the range of 20% to 50% (20-26). In all groups, the concomitant presence of psychological comorbidities had a negative impact on quality of life (21, 23, 26-30).

Although there are well-established interventions targeting anxiety and depression for the general population (31), there are limited data regarding the treatment of these conditions in patients with chronic lung disease. The only studies performed have been done in COPD patients, and these studies have been of varied quality and consequently have a range of results (1). Cognitive behavioural therapy (CBT) has shown potential among patients with COPD, asthma and bronchiectasis (1, 32-37). Pulmonary rehabilitation has the strongest evidence regarding its benefit in these patients, caused mainly through improved physical capacity (38-40). Therefore, the combination of both treatments is promising, with potentially enhanced therapeutic benefit, which would ultimately decrease respiratory symptoms and psychological distress in patients with respiratory disease.

The results of this study will provide data regarding effective treatment for anxiety and depression in patients with chronic lung disease. Furthermore, it tests the benefit of a multidisciplinary team approach for the treatment of psychological comorbidities in the presence of chronic respiratory conditions.

This literature review provides an overview of the prevalence, impact and pathophysiology of anxiety and depression among patients with chronic lung disease and explores screening tools and treatment options. The review will focus on COPD, since the majority of studies have been among this population, and they also form the majority of the population attending pulmonary rehabilitation. Where information is available for other chronic lung conditions, these data will be summarised and discussed.

Prevalence of anxiety and depression as comorbidities in chronic lung disease

COPD has a significant impact on the psychological well-being of people affected. Patients with COPD have a higher prevalence of depression and anxiety than the general population (2) and COPD patients have a relative risk of 1.69 of developing depression (41). The rates of both anxiety and depression may even be more prevalent among COPD sufferers compared with other chronic diseases (42).

The reported prevalence of depression and anxiety are quite varied, depending on the population surveyed (smoking status, COPD severity) and the tools used for screening (43). For patients with stable COPD in primary care settings or respiratory clinics, the prevalence of depression varies widely from 10% to 57% (2, 6), and for anxiety, prevalence ranges from 7% to 50% (2, 5, 6), with many of these patients being unaware of being affected by either condition (44).

Risk factors for increased rates of depression include living alone (45) and gender. Females have a higher rate of both anxiety and depression (6, 46-48), and rates of depression have shown to correlate with severity of dyspnoea as compared with males (47), although the quality of life symptoms has not (18). Increasing severity of COPD is associated with higher rates of depression and anxiety (4, 9, 49); for example, in patients requiring long-term oxygen, 57% were found to have depressive symptoms, and 18% had depression classified as severe (50). End-stage COPD patients undergoing palliative care also have high rates of anxiety (51 to 75%) and depression (37 to 71%) (42).

Other important risk factors for an increased rate of anxiety and depression include patients who have been hospitalised for an exacerbation of COPD or recovering from an exacerbation (11, 51) and severe impairment of physical functioning (5, 6, 45).

As COPD, other chronic lung diseases show a high prevalence of anxiety and depression symptoms. Asthma is historically closely linked to psychiatric diseases and was thought previously to be a psychosomatic illness (27). Large cross-sectional studies showed that depression is more common in people with asthma (17.3 vs 9.1%) (52) and that having asthma increased the chances of having anxiety and depression (odds ratio of 1.5 and 1.6 respectively) (19). The prevalence of major depression in asthma varies from 2% to 26% across the surveys, with prevalence generally between 5–10% (19), while for anxiety the rate is between 11 and 37% (53), with even higher rates in those with severe asthma (54). Community-based epidemiologic studies in youth and adults demonstrate a strong and consistent association between asthma and anxiety disorders (55) with a significant correlation between anxiety and asthma severity (56). Concerning interstitial lung disease (ILD), in a mixed ILD cohort, the prevalence of anxiety and depression was 31% and 23%, respectively (57). Specificity for IPF, the prevalence has been as high as 49% in one study (20). In PAH, the prevalence of depressive symptoms ranged from 15.9% to 55.1 (21, 22, 58), while anxiety was between 28% and 45 % (21, 58), showing a strong association with the level of functional limitation (22) and quality of life (58). For patients with bronchiectasis, 20% to 34% had elevated depression-related scores and 38% to 55% had elevated anxiety-related scores (23, 24, 26), also showing significant association with poor quality of life questionnaire scores (26).

Anxiety and depression are highly prevalent comorbidities in patients with chronic lung disease. In COPD, multiple risk factors have demonstrated to be associated with the prevalence of these comorbidities; however, disease severity seems the most consistent throughout all conditions and may represent the psychological toll suffered by patients living with chronic lung disease.

Pathophysiological mechanisms for anxiety and depression in COPD

Mechanisms for depression:

The aetiology of the association between depression and COPD is not fully understood; however, the relationship is complex and interactive. The most important risk factor for COPD

is smoking. Smoking and depression seem to have a complex bidirectional interaction (59). Depressed individuals are more likely to smoke (60), and find smoking cessation more difficult (60-62). Although the reason to commence smoking is multifactorial with environmental factors playing a significant role (63), the presence of depression and anxiety are independent risk factors to commence smoking (59, 63, 64) (Figure 1). One possible mechanism for part of the increased uptake of smoking is the self-medication hypothesis, where smoking is used as a treatment of depressive symptoms (65, 66). Conversely, smokers are more likely to be depressed (67) (Figure 1), which could be caused by activation of nicotinic acetylcholine receptors (65), or direct inflammatory effects of smoking (68, 69).

Although smoking could have some part to play as a causative factor for depression, depression is still more prevalent among COPD patients than smokers without COPD (48). A possible mechanism could be related to 'overspill' of local lung inflammation in the circulation (68, 70) (Figure 1). It has been speculated that systemic inflammation may play a role in the presence of depression (69, 71). Although there are difficulties in the quantification of inflammatory markers in the 'overspill' theory (68), soluble tumour necrosis factor receptor-1 (sTNFR-1) has shown a strong association with rates of depression in COPD patients (70), while tumour necrosis factor alpha (TNF-α) showed conflicting results (71, 72). It is not clear if the presence of systemic inflammation has a causative association with depression or that it is a marker a specific COPD phenotype; such as frequent exacerbators (70).

Hypoxia is an additional factor that may play a role in the development of depression in COPD (Figure 1). Low arterial oxygen saturation has been shown to be associated with periventricular white matter lesions (73), which are present in patients with depression (74). However, the significance of these findings is contentious since the localisation of subcortical hyperintensity in depressed patients has been found to be variable due to different imaging technologies, lesion definition and measurement techniques (74, 75).

Although smoking, inflammation and hypoxia have a potential impact on the prevalence of depression in COPD, the strongest predictors of depression among patients with COPD are their severity of symptoms and reported quality of life (48) (Figure 1). Functional limitations have been similarly shown to mediate depression in other disorders such as arthritis and heart failure (76). The amount of perceived instrumental support (the need for assistance for activities of daily living) among COPD patients has also been shown to be correlated with depression (77).

COPD and depression

- Hypoxia
- Systemic inflammation
  - 'overspill' theory
- Severity of symptoms
  - The strongest predictor of depression

Smoking

- Bidirectional interaction
- Depressed individuals are more likely to smoke
- Smokers are more likely to be depressed
  - activation of nicotinic acetylcholine receptors
  - Inflammation

$\downarrow O_2$ **Inflammation**
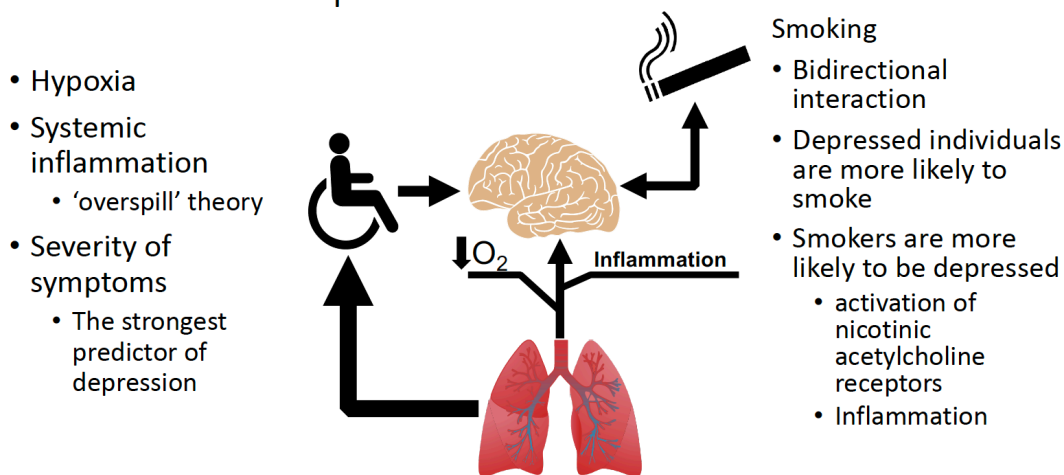
Figure 1. Mechanisms and relations between smoking and depression

Mechanisms for anxiety:

Similarly, to depression, a similar bidirectional interaction is seen between anxiety and smoking. Patients with anxiety are more likely to smoke (78); with the self-medication hypothesis and vulnerability to peer pressure as possible causes (79). On the other hand, smoking could theoretically increase the risk of anxiety thorough nicotine effect on neurotransmitter pathways, and through mechanisms similar to COPD; such as 'overspill' of local lung inflammation and structural brain changes (79).

Several theories have been proposed to explain the overlap of anxiety and panic attack symptoms with COPD (80). Hyperventilation is defined as the exaggerated breathing in excess of metabolic need, causing lowering pressure of carbon dioxide (CO_2) and causing respiratory alkalosis (81, 82). This pattern of breathing can cause dyspnoea in healthy individuals and consequently, panic attacks in those predisposed patients (82).

In panic disorder patients, it is possible to evoke symptoms of dyspnoea and chest pain when infusing lactate or inhaling excessive CO_2 (82). These findings are the basis of the CO_2 hyperventilation model (80). Areas of the brain with intrinsic CO_2/H^+-sensitive neurons such as the ventrolateral surface of the medulla and locus coeruleus are involved in ventilation, but also play a role in panic behaviours. The activation of these areas may concomitantly activate defensive behaviour and precipitate a panic attack (82).

Another relevant theory is the cognitive behaviour model, which is based on the principle that normal bodily sensations are misinterpreted by patients with panic disorder and can consequently cause a panic attack. This misinterpretation is hypothesized to be secondary to a heightened awareness of physiological changes such as dyspnoea and tachycardia (80). A behavioural sensitisation event (trauma) may predispose to panic disorders (82), and post-traumatic stress symptoms are more common in COPD patients with high exacerbation rates (83). The exacerbation is likely the sensitizing event, which consequently could lead to more exacerbations.

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

Association between depression and anxiety symptoms in chronic lung disease and morbidity and mortality

Depression and anxiety are associated with adverse outcomes in patients with chronic lung disease. Increased mortality, exacerbations rate and worse quality of life, have all been described in COPD patients.

Effect on mortality: Among COPD patients, depressive symptoms are associated with increased mortality among hospitalised (11, 12) and community patients (7-9, 84, 85). Some studies of COPD patients have shown an association of anxiety with increased mortality (11-13), whereas others have failed to show any association (8). A recent meta-analysis demonstrated that in COPD patients, comorbid depression and anxiety were associated with increased risk of mortality with relative risks of 2.29 and 1.27, respectively (41).

Importantly, a prospective study by Divo and colleagues, from the Body-mass index, airflow Obstruction, Dyspnoea, and Exercise (BODE) cohort, assessed mortality risk based on the

presence of risk factors. This study demonstrated that anxiety among female COPD patients was associated with a significant increase in mortality, with a hazard ratio of 13.76. This hazard ratio was higher than the risk conferred by coronary heart disease, heart failure, or lung cancer (14). The potential causes of this increased mortality with anxiety are probably multifactorial. One factor is treatment compliance; for example, patients with anxiety and depression are less adherent to medications (86) and are more likely not to complete rehabilitation (87-90). A meta-analysis has shown that patients with depression and anxiety symptoms are three times more likely to be non-adherent to their prescribed medications (91). Alternatively, the presence of symptoms of anxiety and depression correlated with disease severity (4, 9, 49) and may occur secondary to the impact of this disease on patients well-being and physical capacity; consequently, the presence of these comorbidities could be used as another clinical marker of disease severity (14).

Effect on exacerbations: Among COPD patients, exacerbations contribute significantly to morbidity and mortality (92). A narrative synthesis of a systematic review of 20 studies has shown that depression and anxiety increased the risk of hospitalisation for COPD patients (16). A meta-analysis by Laurin *et al.* showed that the relative risk of in-hospital treated COPD exacerbation was 1.12 for depression and 1.18 for comorbid depression and anxiety (93), while a more recent study showed a relative risk of 1.94 (15). A large retrospective cohort study showed a statistically relevant correlation with between the presence of depression and exacerbation with OR of 1.48 (94). Anxiety and depression symptoms were also associated with increased in hospital length of stay for COPD exacerbations (11, 95, 96).

There are multiple possible links between depression or anxiety and increased rates of COPD exacerbation. The impact of symptoms of depression and anxiety could place patients at risk due to non-adherence with treatment (86, 91), and suboptimal success with smoking cessation (11, 93). Depression could have direct effects by impairing the immune system and consequently predisposing to infections (97), leading to increased frequency of exacerbations. Worsened perception of dyspnoea may lead patients to seek medical attention unnecessarily and increase hospital admissions; patients with anxiety and depression during admission have worse dyspnoea scores despite having less severe physiological parameters (e.g. pH, partial pressure of oxygen and CO_2) (98). The meta-analysis by Laurin *et al.* has shown that patients with anxiety were at greater risk for exacerbations that required treatment in the community, whereas those with depression were at higher risk for exacerbations requiring treatment in hospital (93). This

discrepancy could be explained by "early intervention" among anxious patients that could prevent the need for treatment in hospital (93).

Effect on quality of life: The detrimental impact of COPD on quality of life is well-documented. Depression and anxiety symptoms also have a significant impact on quality of life and functional status in many chronic diseases (99, 100). In general, patients with depression and anxiety perceive their health as poorer than the average population (101). Specifically for COPD, the impact of quality of life and functional status is also evident in several studies, independent of the severity of COPD or related comorbidities (18, 49, 100, 102-106). A meta-analysis showed that the presence of depression and anxiety among COPD patients was one the strongest correlations with self-reported health status (107). Comorbid depressive symptoms in patients with COPD are associated with persistent smoking (11), increased symptom burden (11), poorer physical(108) and social functioning (11), and difficulty in performing daily activities (109) and reduced BODE scores (110). Low self-confidence or self-efficacy is also common, which may lead to worsened ability to cope with chronic disease (93, 100). Depression is negatively associated with acceptance of illness, which could negatively impact patient care and decrease treatment compliance (111).

Depression and anxiety symptoms are associated with increased perception of dyspnoea (98, 112-114). The presence of psychological symptoms (mainly depression and to lesser extent anxiety) has an effect on vital exhaustion, defined as a state characterized by fatigue and lack of energy, worsening irritability and feelings of demoralization (115). Fatigue and especially dyspnoea are independently negatively associated with poor health status (107, 116).

The impact of depression and anxiety symptoms are not limited to an individual's lung disease. The presence can influence a person's end of life decisions (117) or may negatively impact partners and their respective relationships (118, 119).

In patients with asthma, clinical anxiety and panic attacks influence symptom perception and asthma management through the effects of anxiety symptoms such as hyperventilation, and indirectly through self-management behaviour (27, 28, 120). In patients with PAH, mental disorders had a negative impact on quality of life, irrespective of severity of disease (21, 58, 121). Similar findings were described in bronchiectasis, with anxiety and depression symptoms predicting a significantly worse quality of life (23, 26). In interstitial lung disease, the quality of

life measure impact depressive symptoms (122), and the presence of depression is significantly correlated with dyspnoea symptoms and sleep quality (123).

Overall, the presence of anxiety or depression have been linked with negative outcomes in patients with chronic lung disease. The presence of these comorbidities throughout all conditions was associated with worse quality of life and symptoms burden. In COPD patients, the presence of these comorbidities are better defined, and of concern, its presence is linked with increased exacerbation rate and mortality.

Diagnosis and screening of depression and anxiety

The gold standard for the diagnosis of depression or anxiety is based on the criteria listed in the DSM-IV and achieved through structured interviews performed by a psychiatrist or a clinical psychologist. There is a positive relationship between self-reported symptoms and the existence of a mental disorder. Therefore, screening instruments that are less costly, faster and easier to administer were developed. These screen tools are seen as useful to make the initial evaluation of mood disorders, and they can also monitor clinical outcomes of mental health treatments (124, 125).

Several screening tools have been validated for use in COPD patients. The Geriatric Depression Scale (GDS) and its 15-item short form (GDS-15) are validated as depression tools (126). The Geriatric Anxiety Inventory (GAI) has been validated for anxiety in COPD patients (127), while the Hospital Anxiety and Depression Scale (HADS) has been validated for both depression and anxiety (128). A systematic review showed consistency between tools and that neither demonstrated superiority to the other (129). Anxiety Inventory for Respiratory Disease (AIR) and Brief Assessment Schedule Depression Cards (BASDEC) are two other scales that have been developed exclusively for COPD (5, 130, 131) (Table 1). For asthma, HADS has been validated for anxiety and depression (132), while the Beck Depression Inventory-II (BDI-II) has been validated for comorbid depression (133).

There are concerns regarding the use of screening instruments due to the risk of false positives caused by the overlap of symptoms (134), and the uncertainty regarding the impact on routine practice (135, 136). Despite the concerns the Global Initiative for Chronic Obstructive Lung Disease guidelines recommend that new COPD patients should have a detailed medical history

including for anxiety and depression (137), although there is no consensus regarding which screening tool is most appropriate for the screening approach for anxiety and depression (138), several seem interchangeable (129).

These tools are useful for screening purposes and have been used extensively to evaluate response to therapy. For many of the studies, changes in scores are difficult to interpret as the minimal clinically important difference (MCID) has not been established. HADS is one of the few tools that the MCID has been established, which was done in the context of patients with cardiovascular disease (139) (Table 1).

Geriatric Anxiety Inventory and Geriatric Depression Scale

COPD patients are generally older. Therefore, tools that screen for depression or anxiety in patients with COPD are likely to be more precise if directed at older individuals. Tools that reduce the confounding effects of somatic symptoms have been developed for older groups and have been used in patients with chronic medical conditions. GAI was designed in Australia for elderly patients. In the study by Cheung et al. (127), GAI was validated for COPD and had a slightly better Area under the Curve (AUC) of 0.83 than HADS-A, which was 0.79. Optimal cut-off points with GAI score of ≥ 3 had a sensitivity of 85.7%, and a specificity of 78%, while the optimal cut-off HADS-A score (≥ 4) had a sensitivity of 78.6%, and a specificity of 70.7% (127). In COPD patients, another study showed that HADS-A had a sensitivity of 71% and a specificity of 81% while BAI had a sensitivity and specificity of 89% and 62%, respectively (140).

GDS was also designed to determine the presence of depression in older patients. When validated for patients with COPD, a cut-off score of ≥ 4 had a sensitivity and specificity of 67% and 82%, respectively (126). GDS was more precise than the initial study of HADS-D, which showed a sensitivity of 62.1%, and a specificity of 62.6% and AOC of 0.66 (141). More recently, a study by Phan (140) removed a question from the HADS-D score and adjusted the cut-off and found an improvement of precision of the test and a new sensitivity of 100% and specificity of 82.6%. This same study also assessed the Beck Depression Inventory (BDI-II) and determined that with the removal of a specific question and an adjustment of the cut-off the sensitivity was now 100% and specificity was 79% (Table 1)

Table 1 - Anxiety and depression screening tools for patients with COPD

Screening tool	Cut-off	Sensitivity	Specificity	MCID	Validation criteria	References
Anxiety						
Hospital Anxiety and Depression Scale (HADS) depression subscale	≥ 4	71 - 78.6%	71 - 81%	Yes	MINI	(127, 139, 140)
Beck Anxiety Inventory (BAI)	≥ 8	89%	62%	No	MINI	(140)
Anxiety Inventory for Respiratory Disease (AIR)	≥ 14.5	80%	75%	No	MINI	(131, 142)
Depression						
Geriatric Anxiety Inventory (GAI)	≥ 3	85.7%	78%	No	MINI	(127)
Hospital Anxiety and Depression Scale (HADS) depression subscale	≥ 8 ≥ 5 (Adjusted HADS-D)	62 - 78% 100% (Adjusted HADS-D)	63 - 81% (82.6%) (Adjusted HADS-D)	Yes	MINI	(139-141)

Geriatric Depression Scale (GDS)	≥ 4	67%	82%	No	MINI	(126)
Brief Assessment Schedule Depression Cards (BASDEC)	≥ 7	100%	93%	No	GMS	(5)
Beck Depression Inventory-II (BDI-II)	≥ 7 ≥ 12 (Adjusted BDI-II)	89% 100% (Adjusted BDI-II)	77% 79% (Adjusted BDI-II)	No	MINI	(140)

Table shows validated screening tools for the diagnosis of anxiety and depression in patients with COPD. Table shows: cut-off for diagnosis of anxiety and depression, sensitivity and specificity of each questionnaire, if each has a determined minimal clinically important difference (MCID) and what was the gold standard used for validation.

Treatment approaches for anxiety and depression in patients with chronic lung disease

Depression and anxiety, when coexisting with chronic lung disease, significantly impact quality of life and functional outcomes. In acknowledgement of the biopsychosocial impact of chronic ill health, the World Health Organization has stated that patients with chronic diseases such as COPD should receive integrated care programs which are centred on the patient rather than just the disease (143). A similar approach is advocated by the Global Initiative for Asthma (GINA) (144). Despite these recommendations, a cross-sectional study of 527 patients with depression and COPD, 18.8% of patients were not treated (145).

Fortunately, interventions targeting these psychological comorbidities are well-established for the general population (31, 146). However, psychological care guidelines are less well developed for patients with chronic lung disease (147). Most studies assess the effects of treating psychological comorbidities among patients with COPD and typically use treatments based on treatment guidelines for depression and anxiety for the broader population (148). These

treatments can be divided into pharmacological and psychological interventions (148). Psychological therapies used in this population have mainly been those that use elements of cognitive and/or behavioural approaches (146), like relaxation therapy (149) and cognitive behavioural therapy (CBT) (150). Other additional therapies for chronic lung diseases have been linked with improvement in anxiety and depression, such as self-management strategies (31) and pulmonary rehabilitation (38-40).

Psychological therapies

For patients with a chronic health condition who are also experiencing clinical or sub-threshold depression, the UK's National Institute for Health and Care Excellence (NICE) recommends the use of low to high-intensity psychosocial interventions depending on the severity of mood symptoms (151). Low-intensity interventions may include individual or self-help programs, or online CBT, while high-intensity interventions are typically individual or group CBT sessions. These recommendations are based on moderate quality randomised controlled trials and the experience and opinion of the Guideline Development Group (151), while the NICE guideline targets general chronic health presentations, good quality studies are somewhat lacking for specific chronic lung diseases. Most studies are for COPD, and in these existing studies, results have been mixed and difficult to compare, due to factors such as: small sample size, varied populations, lack of data on disease severity and differences in the screening tools used to assess these patients. A meta-analysis has described the benefits of the most common psychological interventions - relaxation therapy, CBT and self-management education programs in COPD patient (31). However, Cochrane review regarding the impact of psychological interventions in COPD and asthma could not draw any firm conclusion regarding its role in treatment (34, 152).

Relaxation therapy

Relaxation therapy aims to promote psychological change through techniques that create a relaxed state. Techniques commonly used range from breathing exercises, hypnosis, meditation, body positioning, sequential muscle relaxation, mild forms of exercise and visualisation techniques (153). These methods are used separately or as an element of other psychological treatments or pulmonary rehabilitation (148).

The effectiveness of relaxation-based therapies for COPD was evaluated in a meta-analysis by Volpato *et al.*, which showed slight improvements in symptoms of depression, anxiety and quality of life (149). For patients undergoing a pulmonary rehabilitation program, progressive relaxation techniques administered by tape-recorded classes showed a non-significant improvement in depression and, to a lesser extent, anxiety symptoms at the time of the end of the pulmonary rehabilitation program (154). There have been several smaller studies that have investigated other types of relaxation approaches. One small study using tai chi demonstrated a non-significant improvement of depression, dyspnoea and physical capacity as measured by six-minute walk test results (155). A study examining yoga as the intervention showed a significant improvement in six-minute walk results and functional performance, non-significant improvement in dyspnoea score and quality of life, but no change in anxiety or depression scores (156). In these types of studies, it is often difficult to determine whether the benefit is due to the physical activity or the relaxation components of the treatment.

Some consider mindfulness or mind-body breathing therapy as a form of relaxation therapy. It uses breathing as a focus point, aiming to increase body and mind awareness and consequently reduce stress. In COPD, study results have been mixed. In randomized control trial with patients from a veteran hospital with an average age of 67 years, an eight week intervention did not show any benefit in terms of symptoms or 6-minute walk test, although there was 41% drop rate on the intervention arm (157). A follow-up study by Chan et al., using a similar population and similar intervention showed no significant improvement compared to control. However, for the group of patients that completed at least six sessions, there was a significant improvement in emotional function (158).

Loosely related to relaxation interventions, singing classes have also been used as an intervention in COPD patients. The underlying theory is that singing lessons might improve patient quality of life and/or functional status by offering techniques that address both the

sensory component of dyspnoea (e.g. control of respiratory pattern to reduce hyperinflation) and the affective component (e.g. anxiety and low mood around perceived breathlessness) (159). A moderate-sized study employing singing classes showed improvement in anxiety levels and the physical component of a quality of life questionnaire (160). In a further study by the same researchers, the improvements remained after controlling for the incidental beneficial effects of social interaction amongst the participants. (161). Regarding these less traditional interventions, there is still a lack of clarity about their applicability, their long-term effectiveness, the active component (physical or psychological), and how they may be incorporated into standard care.

Although it has been shown that relaxation therapy does not improve lung function in asthma (162), relaxation therapy has shown benefit in reducing symptoms of asthma in children and adults by achieving a significant degree of relaxation, positive attitude, and better yoga exercise tolerance. There was also a tendency toward lesser usage of beta-adrenergic inhalers (163). For children, relaxation-breathing training combined with a self-management program decreased anxiety symptoms (164). In one study, using the integrated breathing and relaxation technique known as the Papworth method, showed a significant improvement in respiratory and anxiety symptoms at a 12-month follow-up (165). In regards to mindfulness based treatment, it has shown to improve quality of life significantly quality of life but had no impact on lung function or control of asthma (166).

To the best of our knowledge, there are no studies that have examined the effects of relaxation therapies among patients with bronchiectasis and IPF.

The role of relaxation therapy to treat psychological comorbidities in chronic lung disease is still unclear due to mixed results. However, certain techniques such as relaxation methods with pulmonary rehabilitation, yoga or breathing techniques in asthma have shown promising results.

Cognitive behavioural therapy

CBT is a type of psychotherapy used in the management of a range of psychiatric disorders. It is based on an information-processing model in which emotional symptoms are thought to be driven by negatively-biased evaluations of the world, the future, or the self (including bodily sensations) (167). Performed in collaboration between the therapist and the patient, CBT utilises a number of strategies to correct those biased evaluations and provide skills aimed at controlling their symptoms and consequently improving the management of their illness (148).

The use of CBT has gained traction because of its effectiveness in achieving symptomatic relief for patients with chronic illnesses (100, 168). In the COPD population, there have been numerous studies of varying quality and sample size that have shown promising results (37, 169-176). A Cochrane review by Pollok et al. (150), shows a small positive effect upon anxiety and/or depression scores and inconclusive effects of quality of life; however direct comparison is hampered by the fact that interventions varied in regard to the number of sessions, duration of each session and delivery format (group or face to face).

Cost-effectiveness is undoubtedly an important issue, particularly given tightening health budgets, and increasing service imperatives to reduce health care spending. One study has shown that face-to-face CBT is effective and also may be cost-neutral when implemented in COPD patients (168). If other, less expensive approaches are interchangeable to face-to-face, they may be more economically attractive. The use of telephone-based interventions for depression has shown to be just as effective as face-to-face (177-179), has shown to be beneficial for patients with anxiety and depression associated with other chronic diseases (180, 181) and to be cost-saving among patients with COPD (182). A recent study evaluating the role of telephone-based CBT treatment for anxiety and depression for patients with COPD showed a significant reduction in depression but not anxiety symptoms (37).

A novel alternative approach is the use of an Internet-based intervention, which has been shown to be as effective as face-to-face interventions for depression and anxiety (183-185) and maybe even useful for patients with cognitive impairment (186). CBT-based therapies, particularly tightly manualised therapies for sub-clinical anxiety or depression, may not require a fully trained psychologist for its administration, adding to overall cost-effectiveness. A nurse-administered minimal psychological intervention (MPI), based on the principles of CBT and self-management, was used in one study of COPD patients and showed promising results (187).

Not all aspects of CBT therapy may be necessary to produce a therapeutic effect. Purely behavioural interventions can be as effective as CBT for patients with depression (188). They are simpler to administer and theoretically could be used for patients with COPD. A mixed approach using elements of meditation may be helpful, Mindfulness-based cognitive therapy (MBCT) integrates meditation with elements of CBT. The use of MBCT, in conjunction with pulmonary rehabilitation, demonstrated a durable reduction in psychological distress (189).

With regards to asthma, studies of CBT are limited. A recent systematic review provided tentative support to the use of CBT to reduce anxiety symptoms in asthma; however, a definite answer regarding is effectiveness was hindered by the heterogeneity of studies used (190). Similarly, a Cochrane review of CBT in asthma was not able to reach any definitive conclusion regarding the benefit of CBT in reducing asthma symptoms due to the heterogeneity of studies (32-34). A recent feasibility study for patients with comorbid anxiety or depression and severe asthma showed weekly face to face CBT was promising, although it was affected by high drop-out rates (191).

A small pilot study showed that CBT in patients with bronchiectasis significantly improved quality of life scores and psychosocial adjustment (35). To the best of our knowledge, there are no studies that have examined the effects of CBT among patients with ILD.

Despite the heterogeneity of studies, CBT seems to be a promising therapy for patients with comorbid psychological conditions and chronic lung disease. Aspects of this psychotherapeutic approach, like the possibility of flexible forms of therapy such as telephone and internet-based, are additional attractive aspects of this therapy.

Self-management strategies

Self-management programs aim to improve patient care by providing resources and guiding health behaviour change in ways that empower the individual. This empowerment is thought to increase their ability to carry out medical regimens designed to control their chronic disease, improve well-being and decrease exacerbations (192-194). Many self-management programs incorporate aspects of CBT.

The effects on anxiety and depression of self-management programs for patients with chronic health conditions are still unclear, and the results have been modest when compared to more specific psychological interventions (31). Jonker *et al.* found improvement in self-efficacy in older people, but no reduction in health care utilisation or improvement in quality of life (192). In cardiac patients, one study reported a moderate effect of self-management on functional outcomes and depressive symptoms after an acute coronary syndrome (195). For COPD patients, although a review by Kaptein *et al.* reported favourable outcomes for self-management on frequency of hospitalisation, greater exercise tolerance and increased quality of life (196), in the meta-analysis of 29 RCTs by Coventry *et al.*, there was no overall benefit for self-management education alone for anxiety and depression in COPD (31).

A large multicentre randomized trial in COPD patients showed that a self-management intervention reduced exacerbation rates (194). Similarly, a Cochrane review by Lenferink *et al.* (197) showed an improvement in quality of life and a reduction in respiratory-related hospitalization. However, subgroup analysis showed an increased mortality secondary to a respiratory cause in the self-management therapy group. The wide range of measures used across the papers surveyed herein reveals the difficulty in both assessing the effectiveness of interventions within a study and comparing findings across studies reported in the literature.

Finally, active participation in decision making and treatment has been suggested to be beneficial in the management of chronic diseases. Consequently, interventions such as health mentoring (self-management intervention that uses cognitive behavioural techniques to provide skills to improve self-efficacy and disease management, and to change unhealthy behaviours) (198), would be useful in the management of chronic lung disease. Nursing-based mentoring have shown conflicting results with one study showing benefit in quality of life for patients with COPD (199), while other studies have failed to show any positive effect on quality of life (200, 201) or anxiety and depression symptoms (200). Interestingly, increased knowledge gained by a mentoring program caused decreased activity in patients with high anxiety and depression symptoms and had an opposite effect among patients with fewer symptoms (202).

A meta-analysis has shown that case management was the least effective intervention for reducing anxiety and depression when compared to CBT, relaxation or self-management intervention (31).

With regards to asthma, self-management interventions have been shown to reduce symptoms, health care use and adherence to preventive medication. However, interestingly the use of "stress management" techniques was not associated with any symptoms improvement (203). A pilot feasibility study has shown that motivational interviewing (a communication style interned to increase motivation and confidence in engaging in a particular behaviour) has shown improved medication adherence is asthmatics (204).

For bronchiectasis, a Cochrane review assessing self-management techniques that included airway clearance techniques, adherence to therapy, exercise or education had insufficient evidence to assess the efficacy of such self-management approaches (205).

Studies using self-management therapy in patients with chronic disease have demonstrated mixed results regarding health care utilization and quality of life. Regarding improving anxiety and depression symptoms, so far, self-management therapies have not shown to be beneficial.

Pharmacotherapy

Pharmacotherapy is a mainstream treatment for anxiety and depression. Although there is some controversy regarding effectiveness, meta-analyses have shown the overall benefit of pharmacotherapy in the treatment of anxiety and depression (206). In standard clinical practice, antidepressants are the first-line medication used for depression and anxiety (146). Other less common agents used are benzodiazepines, antipsychotics, anticonvulsants and azapirones (148).

Antidepressants work by increasing one or multiple synaptic monoamines, dopamine, serotonin or noradrenaline. They have similar effectiveness but principally differ based on the type and severity of side effects. The main categories are: selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenaline reuptake inhibitors, tetracyclic antidepressants, tetracyclic analogues of mianserin (sometimes called noradrenergic and specific serotonergic antidepressants [NaSSA]), tricyclic antidepressants (TCAs), reversible inhibitors of monoamine oxidase A (RIMAs), monoamine oxidase inhibitors (MAOIs) and melatonergic antidepressants (summarised in Usmani et al. (207)). Antidepressants are a moderately effective treatment for depression in healthy individuals, more so in cases of greater severity and in melancholia, but there is less certainty in physically ill patients. Among this population with subthreshold symptoms of depression (symptoms that are below the DSM-IV

criteria for major depression) or mild to moderate depression, NICE guidelines advice that antidepressants should not be routinely prescribed (151). A Cochrane review of antidepressants (mostly SSRI and TCA), for the treatment of depression or depressive symptoms among physically ill patients, demonstrated a significant improvement among patients with depression or milder depressive disorder, and a positive trend for depressive symptoms and other depressive disorders (208). This Cochrane review also observed that there was a greater long-term improvement for SSRIs compared to TCAs. A study assessing the effects of the SSRI, fluoxetine, in hospitalized patients with depression, showed a positive trend towards improvement of depression symptoms especially for those patients that were more severely ill (209).

In contrast to the wider general population or physically ill, at present, the data for efficacy of pharmacotherapy for anxiety and depression are limited for COPD (210). The main studies have been of SSRIs and TCAs. SSRIs are the first-line pharmacotherapy treatment for depression and anxiety (211). For depression, one moderately large (120 patients) randomized controlled study showed that the use of sertraline significantly reduced depressive symptoms and increased 6-minute walk test (212). While two small studies using paroxetine showed variably significant improvement in quality of life questionnaires (213, 214), anxiety and depression scores and physical capacity after three months (214). A single-blinded open trial study of 57 COPD patients, aiming to assess the acceptability of fluoxetine therapy, showed that over two-thirds of patients declined to use fluoxetine therapy, mostly related to patient biases regarding use of psychiatric medication (215). Of concern, the SSRIs have been associated with increased mortality among older adults with COPD (216).

For TCAs, several small studies have been conducted in COPD. A study by Borson *et al.* showed that nortriptyline was effective in reducing depressive and anxiety symptoms and in increasing physical function (217), although a crossover study of similar size failed to show any benefit when using doxepin for patients with symptoms of anxiety and depression (218). In another study using protriptyline, the majority of the patients did not complete the trial because of the anticholinergic side effects (219). TCAs are no longer first-line treatment for depression or anxiety, and consequently, future trials for this medication class are unlikely (220).

Regarding the treatment of anxiety in COPD patients, a Cochrane review was unable to undertake any meta-analysis due to the poor quality of the studies and very small sample sizes (207). Only four studies were analysed, with two studies using SSRIs, and the other two using

a TCA and azapirones. Two studies using SSRI showed a non-significant reduction in anxiety symptoms (207, 214). The studies using TCA and azapirones did not show any improvement (218, 221).

As was the case for psychological treatment, the overall effectiveness of pharmacotherapy for anxiety or depression in COPD has not been rigorously tested. Studies in COPD have been small, with large heterogeneity of sampling and tools used to assess the efficacy of the treatments. In addition, there is limited evidence regarding the impact of side effects of pharmacotherapy, such as dry mouth and sexual dysfunction (208). Some side effects of treatment (such as dry mouth) may compound adverse effects of medications used for COPD, notably the anticholinergic activity of long-acting muscarinic antagonists (222). In addition, there are issues regarding patient refusal to take antidepressants due to misconceptions regarding depression and addiction, the stigma associated with the disease, and lack of interest and motivation (220). Clearly, much more work needs to be done to test pharmacotherapy for anxiety and depressive symptoms in COPD and to undertake head-to-head comparisons with psychological interventions and combinations of treatments (206).

Concerning asthma, the use of antidepressants in depressed patients with asthma is an intriguing issue. There have been multiple small studies of short duration that have shown a wide range of positive effects. Of these small studies, citalopram has shown decreased steroid use but no effect on depressive symptoms (223), while a randomized control study, evaluated the use of twelve weeks of treatment with escitalopram for patients with depression. This study showed significant improvement in asthma symptoms and corticosteroids use, but only for those with higher symptoms severity and that completed the twelve weeks of treatment; however, there was no significant improvement in depressive symptoms (224). In regards to anxiety and depressive symptoms, the best results were in a small study that used bupropion, which showed significant improvement in anxiety and depression symptoms (225). These results are promising regarding the effects of antidepressants as a class of medication; however, discordant results for the use of antidepressants may be secondary to inherent differences between medications. Adding to this complexity, the antidepressant venlafaxine has in fact been reported to cause an asthma-like picture, with severe airway obstruction (226).

As in COPD and asthma, there is a theoretical benefit of antidepressant use for other chronic lung diseases such as bronchiectasis, IPF and PAH; however, to our knowledge, there are no studies regarding the effectiveness of such medications in these conditions.

Pulmonary rehabilitation

Pulmonary rehabilitation is an essential component of standard care for people who are symptomatic from chronic lung diseases, such as COPD, causing breathlessness and functional impairment (227, 228). Large observational studies of pulmonary rehabilitation participants have reported the prevalence of anxiety symptoms to range between 25% (229) and 40.5% (230), and depressive symptoms to range between 17% (229) and 46.7% (230). The symptoms of anxiety and depression have been associated with program non-completion (229, 231), increased dyspnoea (232), fear of exercise and reduced functional performance both at commencement, completion of pulmonary rehabilitation (233, 234) and reduced adherence to exercise prescription (230). Furthermore, improvement in the symptoms of depression has been associated with improvements in specific domains of health-related quality of life (235). However, it is unclear if the symptoms of anxiety and depression should be addressed prior to entry to a pulmonary rehabilitation program or during the program.

Importantly, the symptoms of anxiety and depression have been shown to improve following completion of comprehensive pulmonary rehabilitation (38-40). In a large randomised controlled trial, participants completing pulmonary rehabilitation were shown to significantly improve symptoms of anxiety and depression when compared to the control group of usual care (39). Studies have also shown that participants with symptoms of anxiety or depression can gain similar improvements in other program benefits arising from pulmonary rehabilitation. For instance, in an observational cross-sectional study, individuals with symptoms of anxiety and depression had similar benefits in exercise capacity and health-related quality of life following pulmonary rehabilitation as participants not experiencing these symptoms (236). Moreover, another observational study reported that participants with greater symptoms of anxiety, in fact, had a more substantial improvement from exercise training following pulmonary rehabilitation (237). Therefore, the recent guideline on pulmonary rehabilitation in adults from the British Thoracic Society states that the psychological status of participants is improved with pulmonary rehabilitation when compared with usual care, and recommends that individuals with symptoms of anxiety and depression should not be excluded from pulmonary rehabilitation (238). The addition of psychological therapy could increase the benefit of pulmonary rehabilitation (174, 189, 239). Two studies have shown that the addition of CBT to pulmonary rehabilitation improved 6-minute walk test (6MWT) (175, 240).

As for the other chronic lung diseases, accumulating evidence supports the usefulness of pulmonary rehabilitation as a treatment. One study in asthma patients has shown that pulmonary rehabilitation has shown to significantly reduce symptoms of both anxiety and depression (241). With regards to interstitial lung disease, pulmonary rehabilitation as shown short term improvement in dyspnoea, quality of life, anxiety and depression scores (242-244); however long term effects were not maintained (242). Similar results regarding health-related quality of life in bronchiectasis patients were also seen in two studies (245, 246).

As per the definition by the American Thoracic Society and European respiratory society "Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors" (247). Possibly due to the physical improvement or social benefit, patients who complete pulmonary rehabilitation have improvement in symptoms of anxiety and depression. However, patients with psychological comorbidities have a lower completion rate, reduced adherence and worse symptoms. Consequently, there is a possible role of treating psychological comorbidities in this population aiming to enhance the benefits of pulmonary rehabilitation in this at-risk population.

Impact of cognitive impairment

The presence of cognitive impairment is increased in asthma (248, 249), COPD (250) and ILD (251), with possible cause the presence of hypoxemia (249, 250). In COPD patients attending pulmonary rehabilitation, the rate of mild cognitive impairment based on MoCA score was 18% and 50% if using complete neuropsychological battery (ENB-2) test (252).

Anxiety is an independent predictor of developing cognitive impairment (253). Depression has also been linked with impaired cognition, affecting mnemonic and executive function, predominantly set-shifting (a measure of attention and cognitive flexibility) (254, 255). Although these psychological comorbidities are associated with cognitive decline, Their impact may be modest in increasing the risk of cognitive decline in COPD patients (250). In COPD, although the causation has not been clearly defined, the association between depression and cognitive decline could be epiphenomenal, possibly related to hypoxemic brain injury (250). To determine such association, longitudinal studies would be required.

What is also unclear is the impact of cognitive deficit in the treatment of anxiety and depression (256). Studies have shown conflicting results regarding the impact of cognitive deficits (especially executive function) and response to SSRI (256). In a study using neuroplasticity-based computerized cognitive remediation, a treatment approach with aspects CBT, Marimoto *et al.* (257) showed that patients with executive dysfunction showed a greater reduction in depression symptoms than controls without. Another concern is the impact of cognitive deficit in other treatments, such as pulmonary rehabilitation. In the study by Cleutjens et al. (258) cognitive impairment was associated with lower rates of pulmonary rehabilitation completion; however, it did not negatively impact reduction in depressive or anxiety symptoms.

Cognitive impairment is more common in patients with chronic lung disease and is associated with anxiety and depression. The presence of cognitive impairment may impact treatment of these comorbidities, and its screening could be useful as a part of the evaluation of patients with chronic lung disease.

Conclusion

Anxiety and depression are common comorbidities among patients with chronic lung disease. The presence of symptoms of anxiety and depression are common and have significant impacts that adversely affect mortality rate, exacerbation rates, hospital length of stay, quality of life and functional status. Pathophysiologically, the mechanism of interaction between psychological comorbidities is better understood in COPD, where the interaction is complex and bidirectional, with the strongest association being the degree of disease severity and symptoms.

The gold standard for diagnosis of anxiety and depression is a structured interview. However, screening tools are validated tools for the initial evaluation of these comorbidities and are useful to assess response to treatment. Regarding treatment, there is no consensus on how to treat these comorbidities. Studies examining specific pharmacological and non-pharmacological treatment of these conditions are encouraging, however, limited to small studies of varying quality. Of the types of possible treatment, currently, CBT has the most promising results for both COPD and asthma, while for other chronic lung condition treatment options have not yet been evaluated. While pulmonary rehabilitation is not specifically a treatment for anxiety and depression, completion of the program is associated with a reduction in anxiety and depression symptoms. Although patients with comorbid anxiety and depression would seem to benefit the most with pulmonary rehabilitation, non-completion rate is the highest in this group.

CBT and pulmonary rehabilitation are the forms of therapy with the strongest evidence to treat anxiety and depression in patients with chronic lung disease. The interesting aspect of these forms of treatment is that they are possibly complementary, as CBT could be incorporated into the pulmonary rehabilitation program and possibly potentiating its effects. This study aimed to answer this question. Through a randomized control trial, we aimed to assess the impact and feasibility of CBT as a treatment for patients with chronic lung disease and anxiety or depression undergoing pulmonary rehabilitation. Results from this study would provide useful data regarding the effectiveness of CBT as a treatment for this group of patients, and possibly determine if a multidisciplinary approach will be synergistic in the treatment of psychological comorbidities in chronic lung disease.

Research Plan and Methodology

Study objectives

Primary objective:

The primary objective is to investigate the benefits of CBT used concomitantly with a pulmonary rehabilitation program for patients with chronic lung disease and coexisting anxiety and/or depression.

Secondary objectives:

1. Analyse the screened population and explore associations with anxiety and depression by calculating correlations with known risk factors.
2. Determine the benefits of CBT in improving quality of life in patients attending pulmonary rehabilitation program with symptoms of anxiety and/or depression.
3. Analyse changes in GAI or GDS for only those with an elevated baseline GAI or GDS, respectively.
4. Determine the impact of CBT in improving physical capacity and attendance in patients attending pulmonary rehabilitation program with symptoms of anxiety and/or depression
5. Determine the effect of mild cognitive impairment in relation to symptoms of anxiety and depression and change of these symptoms over time.

Methodology

Study design:

This study was a prospective, two-armed, randomised controlled trial (RCT), with a longitudinal follow-up of 12 months. Due to the nature of the therapy, the therapists, and participants were not blinded to the conditions. Since the investigator was randomizing, consenting the patients and liaising with the psychology department, blinding of the investigator was not possible. Data was collected at the end of the pulmonary rehabilitation program, and 3 and 12 months following completion of the program for each participant (Figure 2).
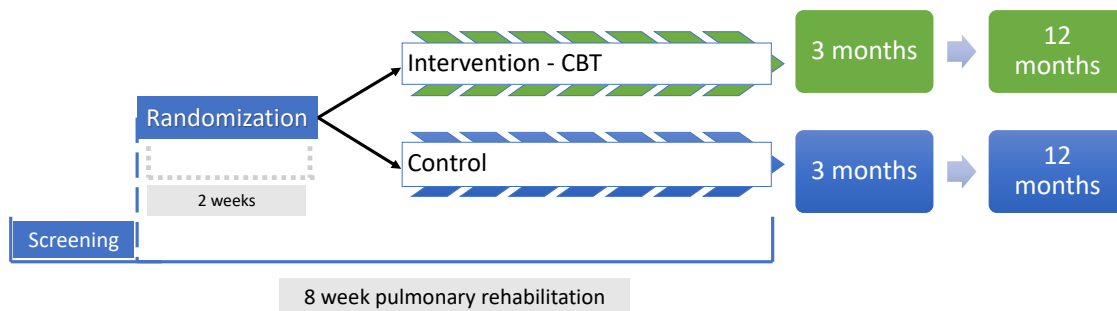
Figure 2 - *Study design*

Patients were randomized 1:1 to intervention or control. Follow-up measurements were taken at the end of rehabilitation, 3 months and 12 months post end of rehabilitation

Participants:

Participants were recruited from the pulmonary rehabilitation program at The Prince Charles Hospital. Patients were invited to participate during the first 2 weeks of pulmonary rehabilitation (Figure 2).

Recruitment:

Written informed consent was obtained from all participants prior to enrolling in the study. Screening forms were sent before the rehabilitation program commenced. Forms review and recruitment were conducted at the completion of the first 2 weeks of the pulmonary rehabilitation program.

Inclusion criteria:

- Adult patients with thoracic-physician diagnosed COPD, asthma, ILD, or bronchiectasis, with consistent symptoms and the following criteria:

    o COPD diagnosis was based on Global Initiative in Obstructive Lung Disease (GOLD) spirometric criteria of forced expiratory volume in 1 second (FEV_1) < 80% predicted and FEV_1/ forced vital capacity (FVC) <70%.

    o Asthma diagnosis was determined by spirometry with an improvement in FEV_1 of at least 12% and at least 200 mL 10-15 minutes after administration of an inhaled rapid-acting β2-agonist, or an improvement in FEV_1 of at least 20% and at least 200 mL after 2 weeks of treatment with an anti-inflammatory agent such as an inhaled corticosteroid or a leukotriene receptor antagonist.

    o ILD diagnosed by thoracic-physician with CT scan, respiratory lung function and/or by histopathology.

    o Bronchiectasis diagnosed by thoracic-physician with confirmed high-resolution CT scan.

AND

- Clinical or subclinical anxiety or depression, defined by GAI score ≥3/20 (127), and/or GDS of ≥4/15 (126).

AND

- Undergoing a pulmonary rehabilitation program

Exclusion criteria:

- Inability to give written informed consent.

- Known psychotic disorder.

- Undergoing psychological therapy

- Cognitive impairment determined by Mini Mental State Examination (MMSE) score of <23 (259, 260)

- Initially, we excluded patients with a Montreal Cognitive Assessment (MoCA) below 26 (261). Due to slower than expected recruitment, we undertook an extensive literature review and found that there was a lack of studies assessing the efficacy of cognitive behaviour therapy for depression and anxiety in patients with mild cognitive impairment, while small studies showed that the CBT is feasible (262, 263) in this cohort. Based on this finding, we applied to change the protocol to allow patients with mild cognitive impairment (normal MMSE and low MoCA) to be eligible, which was approved from July 2016.

  o Studies have demonstrated the feasibility of manualized individual cognitive behavioural therapy in patients with mild to moderate intellectual disability (264).

  o We continued to assess for frontal dementia in the study to assess any possible association with poor outcome.

- Current enrolment in other interventional clinical trials that would potentially interfere with this study.

Data collection:

The following data was collected at baseline assessment during enrolment in the study, face-to-face interview with the participant and review of data from the medical record:

- Demographics: age, sex, ethnicity, education level, smoking history, living alone

- Relevant medical history (list of current multi-morbidities)

- Current medications

- Respiratory function test results

- Computed tomography scan, echocardiogram, right heart catheterization, pathology and sputum microbiology results (where appropriate, based on the chronic lung disease).

- 6-minute walk test

- MMSE score (to exclude cognitive impairment) ranging from 0 to 30 (248).

- MoCA score (to confirm frontal dementia)(261).

- Body-mass index (BMI)

- GDS score (to assess depression) ranging from 0 to 15. A score of 0 corresponds to no symptoms and 15 to maximal symptoms (126)..

- GAI score (to assess anxiety) ranging from 0 to 20. A score of 0 corresponds to no symptoms and 20 to maximal symptoms (127).

- Quality of life/symptom scores, specific to each chronic lung disease:

  - SGRQ for COPD, asthma, ILD and bronchiectasis (265-267).

- Modified Medical Research Council dyspnoea scale (mMRC) (268, 269).

- The body-mass index, airflow obstruction, dyspnea, and exercise capacity index (BODE score) (grading system used as a survival predictor for patients with COPD) (270).

- Measures of participation during rehabilitation based on participants prescribed exercise program based on the American College of Sports Medicine (271).

    o   Minimal pulmonary attendance was defined as > 6 sessions (37.5%).

    o   Successful pulmonary rehabilitation attendance was defined as > 70% of sessions.

Randomisation:

Patients were enrolled in the study and based on their lung condition stratified and randomised on a 1:1: basis to the Intervention group (CBT) or Control group using a computer-generated software package (http://www.randomization.com). Based on previous pulmonary rehabilitation groups, COPD would likely be unevenly distributed in the study; therefore, we elected to randomize patients based on their condition to ensure equal distribution in the Intervention and Control groups. There was no specified block size. Patients were informed of their treatment group following randomisation, at the time of enrolment in the study. Once randomised, both investigators and participants were fully aware of the treatment allocation in an unblinded manner, and there was no sham intervention for the usual care.

Intervention:

The study intervention consisted of CBT conducted by postgraduate psychology interns at The Prince Charles Hospital, under the supervision of a qualified psychologist. The intervention comprised two face-to-face sessions of 1 hour each, during the period of pulmonary rehabilitation, and occurring before or after the sessions. In addition, 4 phone sessions of 45 minutes each were undertaken for counselling, within the first 2 months after the face-to-face sessions. The CBT intervention was tailored to the patient's individual needs. The use of mixed approach with initial face-to-face sessions then telephone-based therapy, was intended to have the established face-to-face therapy to improve therapeutic alliance and minimise the possibility of reduced effectiveness of a solely telephone-based therapy and then continue with telephone-based therapy to maximise adherence.

CBT sessions aimed to build skills in self-management, behavioural activation, identifying and challenging unhelpful thinking, improving relaxation and breathing skills, and promoting effecting coping strategies through training in problem-solving.

Components of the intervention included: Cognitive interventions: Psychoeducation about the interaction between anxiety and physical symptoms (the anxiety-dyspnoea cycle)(272); Challenging and modifying unhelpful cognitions; Problem-solving training to address barriers to effective coping. Behavioural interventions: Relaxation and distraction techniques; Breathing techniques (in conjunction with Pulmonary Rehab team nurses); Reinforcement of activity scheduling; Planning and "pacing" skills; Development of a personalised "good coping plan"(148, 273, 274)

The CBT intervention was based on a manualised approach that was developed by the Psychology Department of The Prince Charles Hospital. One session was videotaped, and a specialist in clinical psychology monitored for adherence to the manual and quality of the intervention.

In addition, as listed below for the Control group, all participants in the Intervention group received standard care for their chronic lung disease and undertook a comprehensive 8-week pulmonary rehabilitation program (Appendix 1). All participants in the Intervention group received a hard copy of the Lung Foundation Australia's Better Living with COPD patient information booklet, which contained a chapter on stress, anxiety and depression (275).

Control group:

The Control group received standard care for their chronic lung disease and undertook a comprehensive 8-week pulmonary rehabilitation with exercise and education (similar to the Intervention group). Each week consisted of 2 sessions on (Monday and Friday) of 2 hours duration; involving 1 hour of exercise and 1 hour of education. The exercise program consisted of a combination of endurance (bike and treadmill/walking) and strength training. Education was undertaken as a group and consisted of issues such as: nutrition, medication management, management of respiratory conditions, speech therapy, and two sessions given by psychologist regarding problem-solving and anxiety and depression in chronic lung disease. All participants in the Control group received a hard copy of the chapter on stress, anxiety and depression, from

the Lung Foundation Australia's Better Living with COPD patient information booklet (similar to the Intervention group). The investigators provided no cognitive behavioural therapy intervention.

Participants in the Control group received telephone contacts with the study personnel at similar times as the Intervention group (i.e. at state times). The telephone call was of shorter duration than the Intervention group, lasting 5-10 minutes, and no intervention beyond the assessment of symptoms was undertaken.

Outcome measures

Primary outcome:

The primary aim was to assess the efficacy of CBT as an effective treatment of anxiety and depression among patients with chronic lung disease attending a pulmonary rehabilitation program. GDS and GAI were used to assess depression and anxiety symptoms, respectively. These screening tools are validated to screen and monitor clinical outcomes in patients with COPD (126, 127). Both GDS and GAI have been validated in older patients. For patients older than 65 years of age, GDS with a score of ≥ 4 of the total score of 15 items had a sensitivity of 67% and specificity of 82% (126). GAI has been validated to determine the presence of anxiety symptoms in older patients. In the study by Cheung et al. of a cohort of patients with COPD and a mean age of 72, a cutoff score of ≥ 3 of the total score of 20 had a sensitivity of 86% and a specificity of 78% (127). At the time of conceptualization of the study, GDS and GAI were the most precise tools for screening anxiety and depression in COPD patients. At the time, studies using HADS scores demonstrated a low specificity of 62% for depression and 70% for anxiety (127, 141). This was thought to lead to an increased susceptibility of enrolling patients with falsely elevated anxiety or depression symptoms, which could lead to a reduces capacity of distinguishing significant change in symptoms with CBT.

Although GDS and GAI tests are not validated for the other conditions, due to the lack of validated options for bronchiectasis and ILD and to simplify the protocol we chose to keep these tools as markers of anxiety and depression for the non-COPD patients. Changes in symptoms were determined by administering GDS and GAI at baseline, end of rehabilitation, 3 months and 12 months after the end of rehabilitation.

Secondary outcomes:

- After the study commencement, clinically important difference (MCID) were determined for HADS (139) and BDI-II (276), which would have been better tools to determine the clinical relevance of the results found. Since GAI and GDS were accurate tests in determining the presence of anxiety and depression, respectively, as a secondary outcome, we aimed to determine the percentage of patients who achieved normal scores.

- Assess quality of life by using a validated quality of life questionnaire. SGRQ is a validated tool to assess quality of life in COPD patients, asthma, ILD and bronchiectasis (265-267).

- Correlate symptoms of anxiety and depression with other relevant clinical aspects, such as: SGRQ, 6-minute walk test, lung function, pulmonary rehabilitation attendance, social status, smoking, BMI and BODE.

- Determine improvement of physical capacity by using a validated marker of physical capacity, 6-minute walk distance at baseline and at the end of pulmonary rehabilitation).

- Pulmonary rehabilitation attendance and participation.

Initially, we excluded patients with a Montreal Cognitive Assessment (MoCA) below 26 (261). After a review of the literature, the presence of mild cognitive impairment was not an excluding factor for successful CBT treatment (262, 263). After revision of the protocol, we performed a subgroup analysis to determine the impact of mild cognitive impairment upon CBT results.

STATISTICS

Statistical analysis:

The analysis was done as an intention to treat. Descriptive statistics were used for exploratory analysis. To determine correlation coefficients between continuous variables, Pearson's correlation was used, and for dichotomous variables, a Point-biserial correlation coefficient was used. To determine differences between the Intervention and Control groups, paired t-tests and χ^2 tests were undertaken for continuous and categorical outcomes, respectively. A p-value (two-tailed) <0.05 was considered statistically significant.

For data collected at multiple points in time, a longitudinal analysis was undertaken. It involved comparing the change in outcomes over time in the Intervention and Control group using repeated measures tests. For these paired measures, a Wilcoxon signed-rank test was used to determine any significant difference over time. Statistical analyses are run using Stata 17 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

Power calculation:

Using Stata (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC), it was calculated that a sample size of 50 intervention and 50 control participants has 80% power at alpha (significance) level 0.05 to detect a 3-fold improvement of anxiety or depression scores, based on the assumption of improvement 10% of the Control group and 33% of the Intervention group.

RESULTS

Screening of patients attending the pulmonary rehabilitation program

Screening: 199 patients attended at least one session of pulmonary rehabilitation between 2 February 2015 and 23 July 2018 at The Prince Charles Hospital. 193 of these 199 patients were screened for symptoms of anxiety and depression as a routine assessment by pulmonary rehabilitation program staff. Based on these scores, 120 (62%) had symptoms of either anxiety or depression, while 73 (38%) had no symptoms of these.

Demographics of screened patients: Regarding the demographics of the patients screened, this was an older group, with more females than males. The majority of patients had COPD, and the remainder had asthma, bronchiectasis and ILD (Table 2). A wide range of lung function impairment was observed (Table 2). 87 (45%) patients had a GAI $\geq$ 3 indicating significant symptoms of anxiety, with 25 patients (13%) having only symptoms of anxiety, while 95 (49%) patients had a GDS $\geq$ 4 indicating significant depressive symptoms, with 33 patients (17%) having only depressive symptoms. 62 (32%) patients had both symptoms of anxiety and depression (Table 1). Anxiety and depression symptoms were prevalent in all conditions, with COPD patients having the highest rates (60% for anxiety or depression), while the other conditions the prevalence was below 40% (Table 2).

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Table 2- Demographics of screened patients attending pulmonary rehabilitation (n=193)

Characteristics	
Age	70.7 ± 9.4 (40 – 90)
Gender	
Male	90 (46.6%)
Female	103 (53.6%)
No symptoms of anxiety or depression	73 (37.8%)
Only symptoms of Anxiety	25 (13%)
Only symptoms of Depression	33 (17%)
Symptoms of both Anxiety and depression	62 (32.1%)
Conditions	
COPD	113 (58.5%)
Asthma	38 (19.7%)
ILD	18 (9%)
Bronchiectasis	24 (12.4%)
Symptoms of anxiety and/or depression per condition	
COPD	
Only symptoms of Anxiety	7 (6.3%)
Only symptoms of Depression	16 (14.4%)
Symptoms of both Anxiety and depression	40 (40%)
Asthma	
Only symptoms of Anxiety	6 (15.4%)
Only symptoms of Depression	7 (17.9%)
Symptoms of both Anxiety and depression	8 (20.5%)
ILD	
Only symptoms of Anxiety	1 (5.5%)
Only symptoms of Depression	4 (22.2%)
Symptoms of both Anxiety and depression	3 (16.7%)
Bronchiectasis	
Only symptoms of Anxiety	7 (29.2%)
Only symptoms of Depression	2 (8.3%)

Symptoms of both Anxiety and depression	3 (12.5%)
FEV$_1$% predicted	
All participants	57.23% ± 24.22 (15 – 129%)
COPD	47.53 % ± 18.14 (15 – 93)
Asthma	59.81% ± 21.86 (31 – 129)
ILD	80% ±19.38 (37 – 107)
Bronchiectasis	66.33% ± 19.45 (39 – 109)
6MWT	367.1 ± 100 (49 – 640)
SGRQ total score	47.2 ± 18.7 (5.48 - 89.7)
BODE	2.8 ± 2.1 (0 – 9)

Note: Plus–minus values are means ±SD (standard deviation). Range for continuous variables is in brackets. Higher SGRQ scores correlate with worse quality of life. BODE is composed of: Body-mass index, airflow obstruction, dyspnea, and exercise capacity index.

Correlations between clinical variables in screened patients: Amongst all screened patients, there was weak to moderate correlation between symptoms of anxiety and depression and poor quality of life based on the SGRQ total score and SGRQ impact scores (which assess social functioning and psychological disturbances) (Table 3). Other correlations tested were generally weak or not statistically significant (Table 3).

GDS and GAI were weakly correlated with >70% compliance with pulmonary rehabilitation sessions, and the group with <70% attendance rate had significantly higher GAI ($p=0.04$) and GDS ($p=0.02$).

There was a weak but statistically significant correlation between failure to attend pulmonary rehabilitation (<6 sessions) and GDS ($p=0.01$) but not for GAI ($p=0.09$), and patients that failed to attend pulmonary rehabilitation had significantly higher GDS scores ($p=0.01$) but not GAI scores ($p=0.1$).

Table 3 - Correlations with anxiety and depression symptoms in screened patients (n=193)

	GDS score	P value	GAI score	P value
SGRQ total	0.52	**<0.01**	0.3	**<0.01**
SGRQ symptoms	0.26	**<0.01**	0.21	**<0.01**
SGRQ impact	0.52	**<0.01**	0.31	**<0.01**
SGRQ activity	0.4	**<0.01**	0.16	0.05
FEV$_1$ % predicted	-0.07	0.38	0.04	0.65
6MWT	-0.26	**<0.01**	0.06	0.42
Minimum oxygen saturation on 6MWT	0.01	0.86	0.05	0.48
BMI	0.22	**<0.01**	0.11	0.15
BODE index	0.23	**<0.01**	0.06	0.46
Smoking				
Current	0.13	0.13	0.01	0.84
Previous	0.25	**<0.01**	0.1	0.18
Pack year	0.14	0.1	0.06	0.46
Lives alone	0.06	0.37	-0.01	0.82
Pulmonary rehabilitation sessions	-0.1	0.19	-0.21	<0.01
Minimal pulmonary rehabilitation sessions (>6 sessions)	-0.18	**0.01**	-0.12	0.09
Pulmonary rehabilitation compliance (>70% attendance)	-0.16	**0.02**	-0.16	**0.04**

Pearson's and Point-biserial correlation were performed continuous and dichotomous variables, respectively. Correlation and p value for each group are shown on the table. Higher SGRQ scores correlate with worse quality of life. BODE is composed of: Body-mass index, airflow obstruction, dyspnea, and exercise capacity index.

Baseline characteristics of patients enrolled

Of the 193 patients screened, 126 patients were eligible to be enrolled in the study, based on a GAI ≥3 and/or GDS ≥4. 22 (17.4%) of these patients declined enrolment in the study, 9 (7.14%) did not attend rehabilitation for further assessment, and another 19 (15.07%) were excluded, as outlined in the CONSORT diagram (Figure 3). 65 patients were enrolled in the study and were randomized (24 patients to Intervention and 41 patients to Control). 10 of 24 patients (41.6%) in the Intervention group failed to complete the intervention. Of these 10, 6 patients (25% of the Intervention group) withdrew from therapy, and 4 patients (16.6% of the Intervention group) failed to attend any CBT sessions and attended further pulmonary rehabilitation sessions. One patient was found not to qualify after review of GAI and GDS. Of those patients who failed to attend, there was an average of one session attended. In the Control group, 1 patient withdrew (2.4%), 2 patients (4.8%) failed to attend 6 or more pulmonary rehabilitation sessions, and 1 patient died during the 8 weeks of attendance at pulmonary rehabilitation (Figure 3).
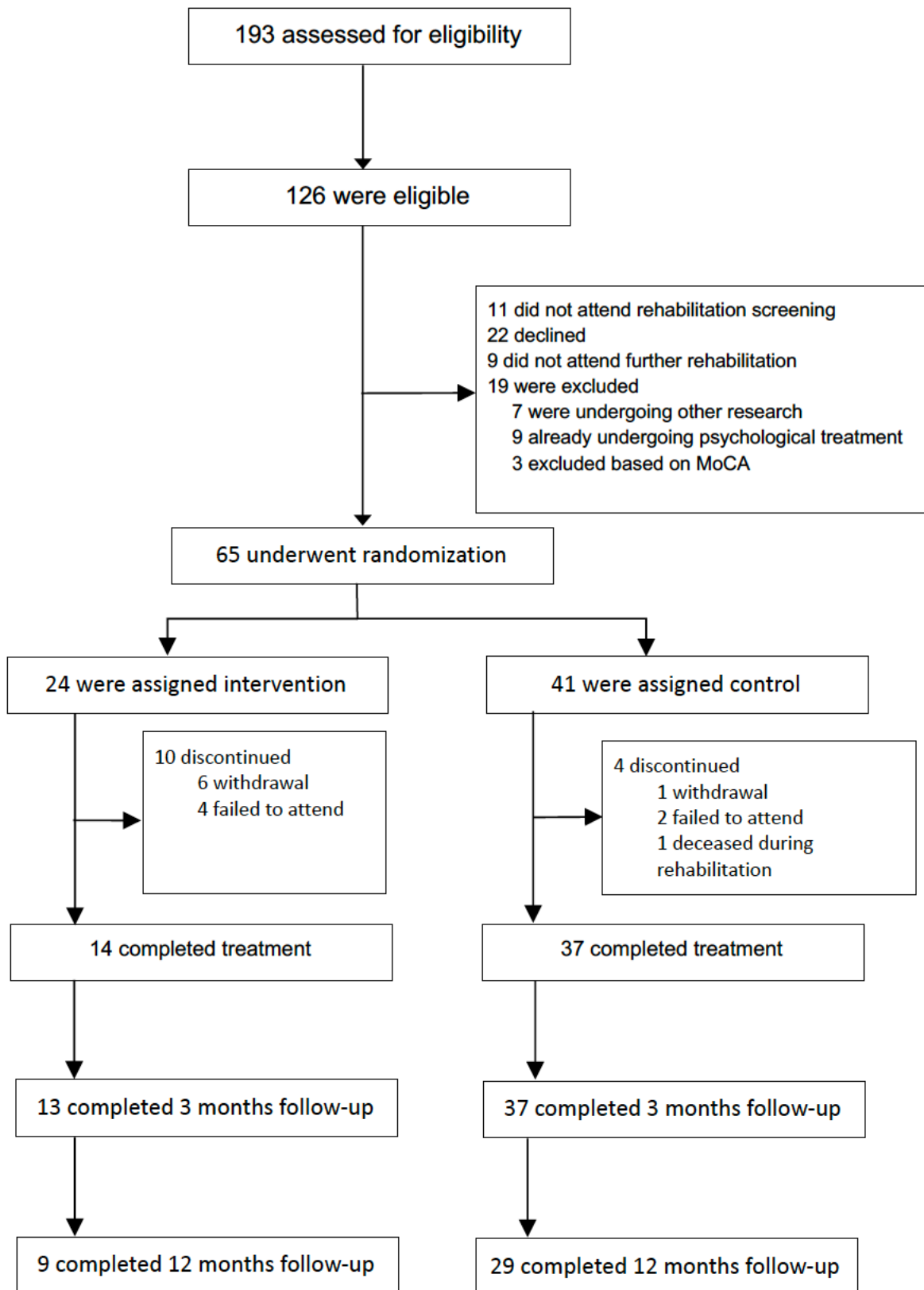
Figure 3 - CONSORT participant flow diagram

Demographic details: The demographic details of the patients enrolled are described in Table 4. Similar to the screened patients, COPD was the most common condition. 22% of patients had known anxiety and/or depression and 22% were on antidepressants, with SSRI being the most common antidepressant. There was no significant difference in antidepressant use between the groups (P=0.06). 20% of the population enrolled had a low MoCA score. There were no statistically significant differences in parameters between the Intervention and Control groups (Table 4).

Table 4 - Demographics of all patients enrolled and by intervention (n = 65).

Characteristics	All patients (n=65)	Intervention (n=24)	Control (n=41)	P value
Gender				
Female (n, %)	39 (60%)	12 (50%)	27 (65.85%)	0.27
Age ± SD (range)	68.8 ± 9.7 (40 – 86)	69.6 ± 11.15 (49 – 86)	68.5 ± 9.2 (40 – 85)	0.65
Conditions				0.69
COPD	49 (75.3 %)	20 (83.3%)	29 (70.7%)	
Asthma	7 (10.7%)	1 (4.0%)	6 (14.6%)	
ILD	3 (4.6%)	2 (8.3%)	2 (4.8%)	
Bronchiectasis	6 (9.2%)	2 (8.3%)	4 (9.8%)	
Anxiety				
GAI ≥3	51 (77.8%)	20 (83.3%)	31 (75.6%)	0.68
Only symptoms of Anxiety	12 (18.4%)	4 (16.6%)	8 (33.3%	
Mean GAI ± SD (range)	7.3 ± 5.6 (0 – 20)	6.7 ± 5.5 (0 – 20)	7.4 ± 5.7 (0 – 20)	0.63
Depression				
GDS ≥4	53 (81.5%)	20 (83.3%)	33 (80.49%)	0.6

Only symptoms of Depression	14 (21.5%)	4 (16.6%)	10 (24.3%)	
Mean GDS ± SD (range)	6.1 ± 3.3 (0 – 15)	6.5 ± 3.3 (0 – 13)	5.8 ± 3.3 (0 – 15)	0.46
Symptoms of both Anxiety and depression	39 (60.0%)	16 (66.6%)	23 (56.0%)	
6MWT (m)	362.2 ± 118.7	338.4 ± 114.8	376.1 ± 118.6	0.23
BODE	3.0 ± 2.3	3.1 ± 2.3	2.8 ± 2.4	0.72
SGRQ baseline		50.2 ± 19.3	56.5 ± 16.9	0.18
Previously diagnosed anxiety or depression	15 (23.0%)	3 (17.6%)	12 (37.5%)	0.15
Only Anxiety	2 (14.3%)	0	2 (18.2%)	
Only Depression	7 (50.0%)	1 (33.3%)	6 (54.5%)	
Both Anxiety and depression	5 (35.7%)	2 (66.7%)	3 (27.3%)	
Antidepressants		2	13	0.06
SSRI	8 (53.3%)	2	6	
SNRI	4 (26.6%)	0	4	
TCA	3 (20.0%)	0	3	
MMSE	29.06 ± 0.99 (26 - 30)	29.2 ± 0.8 (28 – 30)	29 ± 1.1 (26 – 30)	
MoCA	26.6 ± 2.1 (20 – 30)	26.3 ± 2.4	26.7 ± 1.9	0.49
MoCA (<26)	13 (20.0%)	4 (16.6%)	9 (21.9%)	

Notes: *Significant, $p<0.05$.

The demographics of the Intervention group and Control group are expressed separately. T-test was undergone to determine the significance of the difference. There was no statistically significant difference between groups. Higher SGRQ scores correlate with worse quality of life. Higher GAI and GDS correlate with more symptoms of anxiety and depression receptively. Higher BODE scores correlates with increased mortality in COPD patients. Percentages may not add to 100% due to rounding.

Outcomes at the end of the pulmonary rehabilitation program

Within groups: At the end of pulmonary rehabilitation, there was a statistically significant decrease (improvement) in anxiety (GAI) and depression scores (GDS) compared to baseline, for each of the Intervention and Control groups (Table 5). There was no statistically significant difference in quality of life (SGRQ) scores.

Between groups: There was no statistically significant difference in the changes in GAI or GDS scores between the Intervention and Control groups (Table 6). The waterfall plot of changes of scores for individual patients shows that GDS improved for almost all patients that attended CBT, which was not the case of the control patients (Figure 4).

Patients with high symptom scores at baseline: For those patients with symptoms of depression at baseline (GDS score ≥4/15), there was a significant improvement in GDS by the end of rehabilitation, within each of the Intervention ($p<0.01$) and Control groups ($p=0.01$) (Table 7), which was not statistically different between these groups ($p=0.16$). The median GDS score was 5; when considering response of treatment in patients with GDS above this cut-off, there were significant improvements within both the Control ($p=0.03$) and Intervention ($p<0.01$) groups, but no significant difference in changes of scores between the groups ($p=0.058$).

For patients with symptoms of anxiety at baseline (GAI score ≥3/20), there was a significant improvement in GAI by the end of rehabilitation, within each of the Intervention ($p=0.01$) and Control groups ($p<0.01$) (Table 8), which was not statistically different between these groups ($p=0.16$). When analysing patients above the median GAI score (GAI ≥ 6), there was a significant reduction of this score within both the Control and Intervention groups, with no significant difference between the groups ($p=0.42$).

For SGRQ, there was no significant improvement in GAI and GDS scores for both Control and Intervention groups (Table 6). If assessing SGRQ for those patients with an elevated baseline GDS or GAI, there was also no significant improvement SGRQ after rehabilitation (Table 6 and Table 7).

6MWT and attendance: 58% of patients had an improvement in 6MWT after pulmonary rehabilitation. However, there was no overall significant improvement from baseline for either the Control or the Intervention group (Table 5), with waterfall plot showing a similar distribution of change the control and CBT groups (Figure 4). The Intervention group showed a significant

increase in the number of sessions of pulmonary rehabilitation attended, with the average number of attended sessions in the Intervention group being 14.0 (± 1.7) while in the Control group was 12.4 (± 2.6) (diff = 1.59; 95% CI, 0.11 to 3.07; p = 0.03).

Table 5 - Within-group analyses showing changes in GDS, GAI, SGRQ and 6MWT scores in the Intervention and Control groups.

End point (n=14)	Intervention Median (IQR)	Patients	Difference (95% CI) from baseline	P value	Control Median (IQR)	Patients	Difference (95% CI) from baseline	P value
GDS								
Baseline	5.5 (4 – 10)	19			5 (4 – 8)	37		
End of rehabilitation	3 (1 – 5)	19	-3.1 (-4.39 to -1.7)	**<0.01**	4 (1 – 7)	37	-1.3 (-2.4 to -0.27)	**0.01**
3 months	4 (3 – 5)	15	-1.46 (-4.17 to -0.75)	**<0.01**	5 (3 – 8)	37	-0.6 (-1.31 to 0.28)	0.22
12 months	3.5 (2.5 – 5.5)	12	-1.6 (-3.29 to -0.03)	**0.04**	5 (2 – 8)	29	-0.5 (-1.41 to 0.38)	0.25
GAI								
Baseline	7.5 (3 – 8.5)	19			7 (3 – 12)	39		
End of rehabilitation	3 (0 – 6)	19	-2.6 (-4.69 to -0.57)	**0.01**	3 (0 – 8)	39	-2.6 (-4.16 to -1.14)	**<0.01**
3 months	2 (0 – 8)	15	-1.6 (-5.1 to 0.31)	0.07	5 (2 – 11)	39	-0.8 (-2.5 to 0.2)	0.14
12 months	5 (1.5 – 11)	12	-0.9 (-4.98 to 3.31)	0.66	3 (2 – 11)	29	-1.1 (- 3.2 to 0.84)	0.24
SGRQ								
Baseline	49.7 ± 18.5	19			59.8 (43.8 - 68.6)	37		
End of rehabilitation	53.8 (32.9 - 64.8)	19	-6.35 (-17.34 to 4.63)	0.24	52.4 (37.0 - 61.5)	35	-6.0 (-14.84 to 2.84)	0.17
3 months	44.8 (29.4 – 59.5)	13	-3.8 (-15.12 to 7.4)	0.47	51.7 (38.9 – 62.9)	32	-5.6 (-15.33 to 4.04)	0.24
12 months	45.9 (32.8 – 61.2)	11	4.2 (-11.52 to 20)	0.56	50.2 (30.5 – 63.5)	27	-8.2 (-19.35 to 2.93)	0.14

6MWT

Baseline	320 (266 – 430)	19			375 (307 – 465)	32		
End of rehabilitation	339.5 (255 – 427)	19	- 3.4 (-24.4 to 16.6)	0.7	382.5 (300 – 459)	32	14.7 (-5.7 to 35.1)	0.15

An intention-to-treat analysis was performed using a paired t-test to determine change over time. P values compared anxiety, depression and quality of life questionnaires at End of rehabilitation, 3 and 12 month follow-up, with Baseline. Higher SGRQ scores correlate with worse quality of life. Higher GAI and GDS correlate with more symptoms of anxiety and depression receptively. Significant P values (<0.05) were bolded.

Table 6 - Group analyses showing between Intervention and Control groups for GAI, GDS and SGRQ scores, at the End of rehabilitation, 3 months and 12 months.

End point (n=14)	Intervention group Difference from baseline Median (IQR)	Number of patients	Control group Difference from baseline Median (IQR)	Number of patients	Intervention difference - Control difference (95% CI).	Between group comparison P value
GDS end of rehabilitation	-3 (-5 to 0)	19	-1 (-3 – 0)	37	-1.7 (-3.45 to 0.13)	0.053
GDS 3 months follow-up	-1 (-2.5 – 0)	12	-0 (-3 – 0)	35	-0.7 (-2.2 to -0.68)	0.29
GDS 12 months follow-up	-1 (-4 – 1)	11	-0.5 (-2 – 1)	26	-1.2 (3.01 to 0.66)	0.2
GAI end of rehabilitation	0 (-7 – 1)	19	-1.5 (-6 – 0)	38	-0.1 (-2.5 to 2.55)	0.98
GAI 3 months follow-up	0 (-5.5 – 1.5)	12	0 (-3 – 2)	37	-0.8 (-3.43 to 1.93)	0.59
GAI 12 months follow-up	-2 (-5 – 3)	11	-2.5 (-4 – 1)	26	0.1 (-4.21 to 4.47)	0.74
SGRQ end of rehabilitation	-6.8 (-21.2 - 14.3)	19	-5.6 (-26.9 - 13.3)	35	0.3 (-14.51 to 13.8)	0.96
SGRQ 3 months follow-up	-0.29 (-16.0 - 13.4	12	-11.7 (-28.8 – 4.9)	29	-4 (-13.5 to 21.5)	0.64
SGRQ 12 months follow-up	5 (-21.1 - 19.3)	10	-7.9 (-19.8 - 12.6)	24	-8.7 (12.54 to 30.1)	0.06

An intention-to-treat analysis was performed using an independent t-test between the Intervention and the Control groups at the End of rehabilitation, 3 months and 12 months follow. Up. Higher SGRQ scores correlate with worse quality of life. Higher GAI and GDS correlate with more symptoms of anxiety and depression receptively. Significant P values were bolded.

Figure 4 - Waterfall charts demonstrating changes of GAI, GDS, SGRQ and 6MWT in each individual patient that attended cognitive behavioural therapy and Control groups before and after pulmonary rehabilitation.

Table 7 - Within-group analyses showing changes in GDS and SGRQ scores for only patients with elevated GDS at baseline and the percentage that reached normal GDS scores.

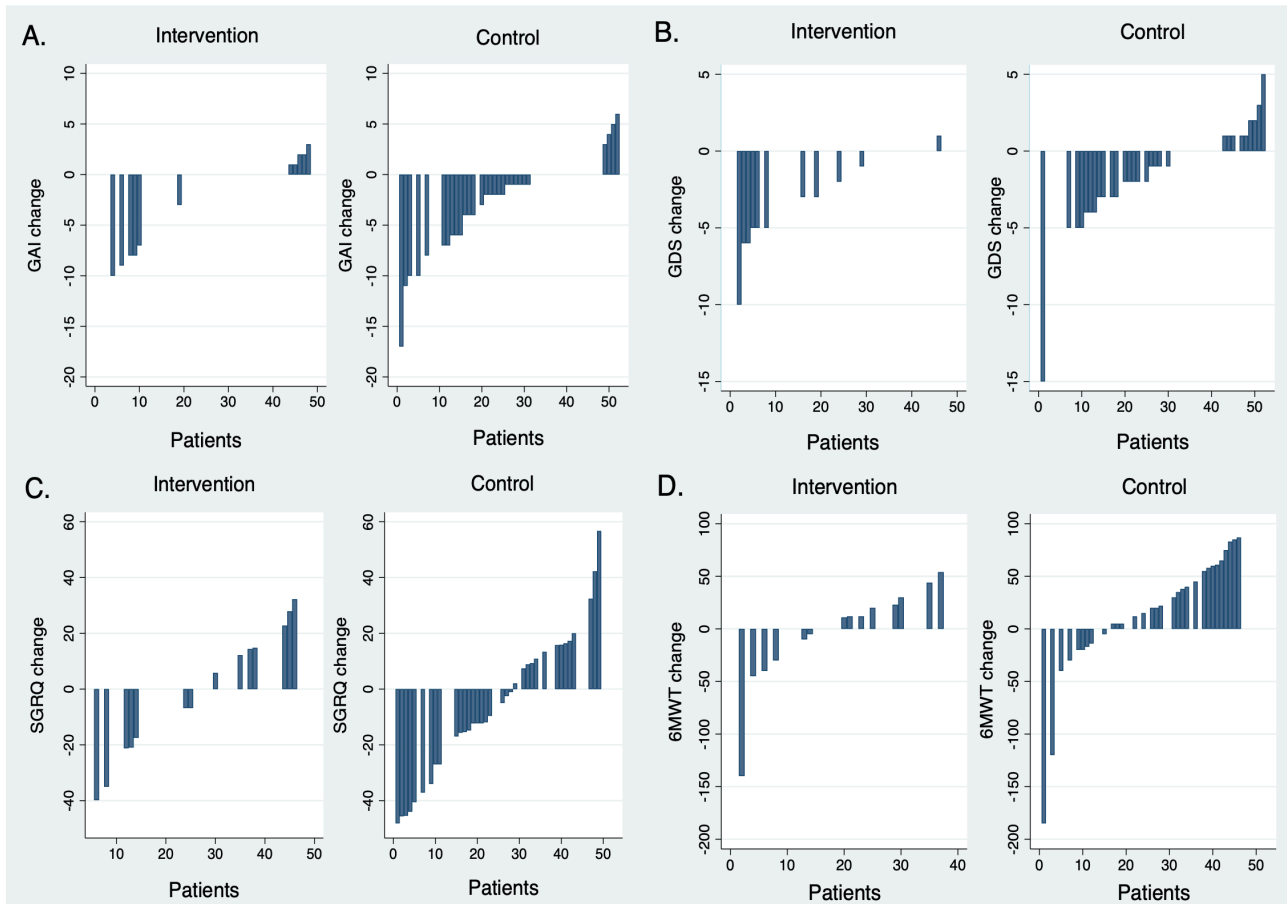| End point	Intervention (n=14)	Difference (95% CI) compared to baseline	P value	Control (n=37)	Difference (95% CI) compared to baseline	P value
GDS (patients with GDS ≥4)	**Median (IQR)**			**Median (IQR)**		
Baseline	6 (4 - 10)			6 (4 - 10)		
End of rehabilitation (n = 62)	4 (2 -5)	-3.3 (-4.74 to - 1.84)	**<0.01**	5 (2 – 8)	-1.7 (-3.0 to -0.3)	**0.01**
3 months (n = 44)	4 (3 - 5)	-2.6 (-4.4 to -0.83)	**<0.01**	5.5 (3 – 8)	-0.8 (-1.76 to 0.15)	0.09
12 months (n = 32)	4 (3 - 5)	-1.7 (-3.66 to 0.26)	0.08	7 (4 – 8)	-0.5 (-1.75 to 0.70)	0.38
SGRQ (for patient GDS≥4)	**(Mean ± SD)**			**(Mean ± SD)**		
Baseline	46.5 (28.28 – 64.8)			60.5 (37.77 – 69.86)		
End of rehabilitation (n = 62)	45.5 (42.65 – 61.27)		0.55	54.3 (45.37 – 64.53)		0.63
3 months (n = 44)	50.6 (34.92 – 61.78)		0.93	53.88 (39.53 – 64.40)		0.60
12 months (n=32)	64.8 (52.91 – 71.24)		0.14	53.3 (38.44 – 71.42)		0.63
Patients achieving normal GDS (GDS <4)	Number (%)			Number (%)		
End of rehabilitation (n = 43)	10/18 (55.5%)			10/30 (33.3%)		
3 months (n = 42)	9/17(52.9%)			9/31 (29%)		
12 months (n = 32)	4/10 (40%)			5/21 (23.8%)		

An intention-to-treat analysis was performed using a paired t-test to determine change over time. P values compared depression and quality of life questionnaires at End of rehabilitation, 3 and 12 month follow-up, with Baseline. Patients with a normal GDS at baseline were excluded from the analysis. Significant P values (<0.05) were bolded.

Table 8 - Within-group analyses showing changes in GAI and SGRQ scores for only patients with elevated GAI at baseline and the percentage that reached normal GAI scores.

End point	Intervention (n=14)	Difference (95% CI) compared to baseline	P value	Control (n=37)	Difference (95% CI) compared to baseline	P value
GAI (for patient GAI≥3)	**Median (IQR)**			**Median (IQR)**		
Baseline	7.0 (3.5 – 8.5)			9 (5 – 15)		
End of rehabilitation (n = 62)	4.0 (0.5 – 7)	-3.3 (-5.86 to -0.79)	**0.01**	5 (3 – 11)	-3.37 (-5.29 to – 1.46)	**<0.01**
3 months (n = 44)	5.5 (3.0 – 8.5)	-2.7 (-5.9 to 0.37)	0.07	6.5 (4 – 11)	-1.63 (-3.31 to 0.04)	0.06
12 months (n = 32)	5.0 (1 – 13)	-1.6 (-7.36 to 4.03)	0.51	6 (2 – 12)	-1.47 (-4.03 to 1.08)	0.24
SGRQ (for patient GAI≥3)						
Baseline	52.3 (28.28 - 64.64)			63.5 (48.50 - 72.13)		
End of rehabilitation (n = 62)	43.6 (26.86 – 59.61)		0.27	53.95 (36.10 – 64.77)		0.13
3 months (n = 44)	42.6 (30.74 – 60.64)		0.32	52 (39.53 – 61.08)		0.22
12 months (n = 32)	56.9 (52.22 – 71.12)		0.68	52.1 (26.93 – 69.80)		0.23
Patients achieving normal GAI (GAI<3)	Number (%)			Number (%)		
End of rehabilitation (n = 41)	6/16 (37.5%)			7/29 (24.1%)		
3 months (n = 40)	8/15 (53.3%)			5/30 (16.6%)		
12 months (n = 30)	2/9 (22.2%)			6/23 (26.1%)		

An intention-to-treat analysis was performed using a paired t-test to determine change over time. P values compared anxiety and quality of life questionnaires at End of rehabilitation, 3 and 12 month follow-up, with Baseline. Patients with a normal GAI at baseline were excluded from the analysis. Significant P values (<0.05) were bolded.

Outcomes at 3 months follow-up

Within groups: At 3 months follow-up after the end of pulmonary rehabilitation, there were 50 patients assessed. Of those, 13 patients (26%) were in the Intervention groups, and 37 (74%) were in the control group. There was a sustained improvement in GDS in the Intervention group ($p < 0.01$) that was not demonstrated in the Control group (Table 5) (Figure 5). There was no statistically significant improvement in GAI (Figure 5) and SGRQ from baseline in both the Intervention and Control groups (Table 5).

Between groups: At 3 months, there was no statistically significant improvement in GDS, GAI and SGRQ scores between the Intervention and the Control groups (Table 6).

Patients with high symptom scores at baseline: Analysing GDS change for those with elevated GDS at baseline, there was a sustained improvement in scores at 3 months follow-up in the Intervention group ($p<0.01$), which was not demonstrated in the Control group ($p=0.09$) (Table 7); and there was no significant difference between groups ($p=0.3$). Patients with an elevated GDS did not demonstrate a significant improvement in SGRQ by 3 months.

For patients with an elevated GAI score at baseline, there was no significant improvement in GAI in the Intervention group ($p=0.07$) and the Control group ($p=0.06$)(Table 8); which was not significantly different between the groups ($p=0.13$). There was no significant improvement SGRQ at 3 months follow-up in this population, in both Intervention and Control groups (Table 8).

Outcomes at 12 months follow-up

Within groups: At 12 months follow-up after the end of pulmonary rehabilitation, there were 38 patients assessed. Of those 9 patients (23.7%) were in the Intervention groups, and 29 (76.3%) were in the control group. There was a sustained improvement in GDS in the Intervention group (p = 0.04) that was not demonstrated in the Control group (Table 5) (Figure 4). There was no statistically significant improvement in GAI (Figure 5) and SGRQ from baseline in both the Intervention and Control groups (Table 5).

Between groups: At 12 months follow-up, there were no statistically significant differences in the changes in GAI, GDS and SGRQ scores between the Intervention and Control groups (Table 6).

Patients with high symptom scores at baseline: For patients with an elevated GDS, there was no significant sustained improvement in scores at 12 months follow-up in the Intervention group (p=0.08) and the Control group (p=0.38) (Table 7); There was no significant difference between the Intervention and Control Groups (p=0.48). For those with an elevated GDS, there was no significant improvement in SGRQ in this group at 12 months for both the Intervention and control groups (Table 7).

For patients with an elevated GAI, there was no significant improvement in GAI at 12 months for both the Intervention and Control groups (Table 8), which was not significantly different between the groups (p=0.84). There was no significant improvement in SGRQ in both Intervention and Control groups, for those with an elevated GAI (Table 8).
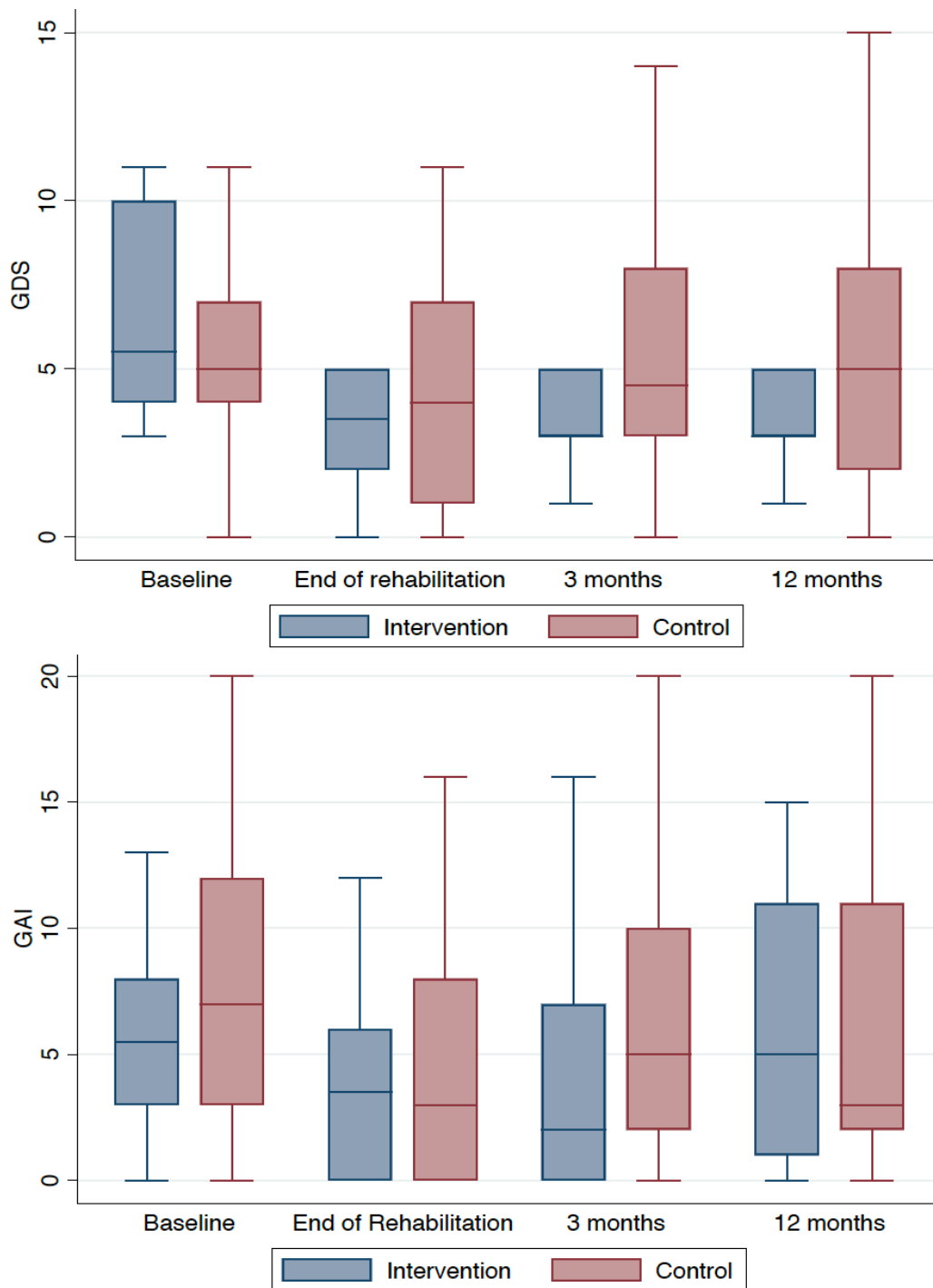
Figure 5 - *Box plot graph of Geriatric Anxiety Inventory (GAI) and Geriatric Depression Scale (GDS) over time.*

Graph A shows a box plot with GDS over time. Graph B shows a box plot with GAI over time. Underneath are the number of patients analysed in each group at each follow-up time.

Impact of mild cognitive impairment

There were 13 patients (20%) with a MoCA consistent with mild cognitive impairment (score of <26). Of these, 4 patients received CBT. At the end of rehabilitation, patients with mild cognitive impairment failed to demonstrate an improvement in GDS, GAI and SGRQ (p=0.61); while the patients with a normal MoCA had an improvement in GDS (p<0.001), GAI (p<0.001) but not for SGRQ (p=0.08) (Table 8). There was no significant difference in GAI (p=0.39), GDS (p=0.19) and SGRQ (p=0.79) between those with low MoCA and those with normal MoCA.

At 3 and 12 months follow-up after the end of pulmonary rehabilitation, there were 10 patients with a low MoCA score. At 3 months follow-up, there was no significant difference in GDS and SGRQ. While those with a normal MoCA score, there was an improvement in GDS (p=0.01), and GAI (p<0.001) but not for SGRQ (p=0.08) TTable 8). There was no significant difference in GAI (p= 0.66), GDS (p=0.95) and SGRQ (p=0.31) between those with low MoCA and those with normal MoCA.

At 12 months follow-up after the end of pulmonary rehabilitation, there was no significant difference for GDS, GAI (p=0.46) and SGRQ for those with a low MoCA score. Patients with a normal MoCA demonstrated a sustained improvement of GDS (p=0.02) and GAI (p=0.01) but not for SGRQ (p=0.38) (Table 8). There was no significant difference in GAI (p= 0.66), GDS (p= 0.95) and SGRQ (p=0.31) between patients with low and normal MoCA at 12 months follow-up.

Table 8. Within-group analyses of GAI, GDS and SGRQ overtime for patients with mild cognitive impairment and a patients without mild cognitive impairment.

End point (n=14)	Low MoCA (N=13)	Difference (95% CI)	P value	Normal MoCA (N=52)	Difference (95% CI)	P value
GAI	**Median (IQR)**			**Median (IQR)**		
Baseline	6 (4 – 8)			7 (3 – 12.5)		
End of rehabilitation	5 (2 – 9.5)	-1.6 (-4.7 to 1.53)	0.28	3 (0 – 7)	-2.9 (-4.23 to -1.63)	<0.001
3 months	6.5 (2 – 11)	-0.5 (-2.91 to 1.91)	0.65	4.5 (1 – 9)	- 2.9 (-4.23 to - 1.63)	<0.001
12 months	9.5 (3 – 13)	1.8 (-3.49 to 7.09)	0.46	3 (1 – 10)	-2 (-7.75 to - 3.33)	0.02
GDS						
Baseline	6 (4 – 7)			5 (4 – 10)		
End of rehabilitation	5 (3 – 7)	-0.7 (-2.54 to 1.04)	0.37	3 (1 – 5)	-2.2 (-3.18 to -1.25)	<0.001
3 months	4.5 (2.5 – 7.5)	-0.6 (-2.23 to 0.89)	0.36	4 (3 – 7)	-1.2 (-2.05 to -0.27)	**0.01**
12 months	6 (2 – 8)	-0.3 (-2.73 to 2.13)	0.78	4 (2 – 7)	-1 (-1.8 to -0.26)	**0.01**
SGRQ	**(Mean ± SD)**			**(Mean ± SD)**		
Baseline	53.7 ± 19.22			54.7 ± 17.8		
End of rehabilitation	50.13 ± 14.9	-13.7 (- 18.76 to 11.64)	0.61	47.9 ± 18.66	-6.8 (-14.53 to 0.97)	0.08
3 months	55 ± 14.56	2.8 (-12.77 to 18.39)	0.69	46.7 ± 19.1	-7.2 (-15.66 to 1.25)	0.09
12 months	58.7 ± 10.78	5.5 (-10.55 to 21.52)	0.45	49.1 ± 22.8	-7.7 (-18.56 to 3.08)	0.15

Paired t-test was performed to determine change over time. P values compared anxiety, depression and quality of life questionnaires at End of rehabilitation, 3 and 12 month follow-up, with Baseline. Higher SGRQ scores correlate with worse quality of life. Higher GAI and GDS correlate with more symptoms of anxiety and depression, receptively. Significant P values (<0.05) were bolded.

Discussion

Overview of results

This study did not show a significant improvement in GAI, GDS or SGRQ scores when comparing CBT added to pulmonary rehabilitation or pulmonary rehabilitation alone. There was a large proportion of patients with anxiety and depression among patients attending pulmonary rehabilitation. GDS was correlated with poor quality of life, 6MWT, BMI and not FEV_1, while GAI was only correlated with poor quality of life. Depression was also correlated with poor attendance. By the end of pulmonary rehabilitation, there was an improvement in GAI and GDS independent of treatment. In the Intervention group, GDS was lower than baseline at 3 and 12 months, which was not the case for the Control group. However, there was no significant difference in GDS between the Intervention and Control groups even when only analysing those with an elevated GDS at baseline. The improvement in GAI seen at the end of rehabilitation was not present at 3 or 12 months for both Intervention and Control groups. There was no significant improvement in SGRQ at any point during the study for patients receiving or not CBT. Sub-group analysis of a small number of patients with mild cognitive impairment showed no improvement in GDS and GAI at any follow-up point. There was a significant increase in attended pulmonary rehabilitation sessions in the Intervention group, compared to the Control group.

Screened population

Incidence of anxiety and depression symptoms

In our study, patients attending pulmonary rehabilitation demonstrated a high incidence of anxiety (44%) and depression symptoms (48%). COPD was the largest cohort, and the incidence of anxiety in this subgroup was 42%, while depression was 50%, which was somewhat higher than previous studies of similar patients (88, 230). The high incidence of psychological comorbidities in the rehabilitation group likely reflects patients with severe and symptomatic disease, which are generally the reasons that prompted a referral to pulmonary rehabilitation in the first instance. Because of the high

incidence of neuropsychological impairment and the impact of these comorbidities on these patients; routine screening before pulmonary rehabilitation may be a beneficial step in the optimization of treatment in these patients.

Correlations between anxiety and depression symptoms and other clinical variables

Our study showed a correlation between higher GAI and GDS scores and impaired quality of life, which has been similarly demonstrated in previous studies (102, 107). Although the severity of COPD has been associated with rates of anxiety and depression (9, 40), we did not find a consistent correlation between physiological markers of COPD severity and anxiety or depression symptoms.

In contrast to a previous study, anxiety and depression were not correlated with living alone (277). We did find an expected correlation between tobacco history and depression. Although epidemiological studies have been heterogeneous, they have generally found an increased risk of anxiety among patient with a previous or current history of nicotine use (78), which was not demonstrated in our group. This finding could be secondary to other factors (such as quality of life and shortness of breath symptoms) playing a more significant role in the development of anxiety symptoms among patients with severe lung disease.

Anxiety symptoms were not correlated with 6MWT distance, level of oxygen saturation during 6MWT, severity of lung disease based on FEV1 or BMI. The only significant correlation with anxiety was with quality of life, as assessed by the SGRQ. The perceived impact of the disease, the possible trauma associated with the presence of a severe lung disease and life-threatening events associated with exacerbations of these conditions (83), may play a more significant impact on the psychological well-being of patients with respiratory conditions than the physical impact of these respiratory conditions.

6MWT and BMI but not FEV1 were correlated with depression symptoms. These correlations have been demonstrated in a previous study (40), and interestingly, a reduction in body fat mass after rehabilitation was associated with improvement in

depression symptoms (40). This association could be bidirectional in nature, as depression is associated with decreased activity leading to elevated BMI, but also an elevated BMI is associated with increased inflammation which could lead to depressive symptoms (68). Anxiety, depression and quality of life reflect the negative impact of chronic lung disease on each patient's psychosocial well-being. This impact is not trivial, and all three are associated with increased mortality (14, 16, 269). Consequently, screening for anxiety and depression, similarly to quality of life, maybe an important aspect in prognostication of patients with chronic lung disease.

Impact of anxiety and depression symptoms and pulmonary rehabilitation attendance

Similar to previous studies, the presence of depression was associated with poor pulmonary rehabilitation attendance and completion (87-90, 231). Non-attendance to rehabilitation programs may reflect poor overall compliance and adherence to other forms of treatment, as depression has been associated with poor medication compliance (91). The cause is unclear, but lack of energy, motivation and poor perception of self-worth could all contribute to the lack of engagement to treatment in this population. This is unfortunate since due to the negative impact of anxiety and depression and the positive effects of pulmonary rehabilitation for these patients, they are a group who could benefit the most from engagement with treatment.

Treatment effects

Effects of pulmonary rehabilitation on anxiety and depression symptoms

This study evaluated the effects of CBT as an addition to pulmonary rehabilitation for patients with chronic lung conditions of moderate to severe severity and symptoms of anxiety and depression. As demonstrated in previous studies (40, 278, 279), there was a significant reduction in symptoms of anxiety and depression in all patients at the end of pulmonary rehabilitation. However, in contrast to those studies, there was no improvement in SGRQ. The study by Catalfo *et al.* (40), similarly to our study, was

directed at patients with symptoms of anxiety and depression but involved an intensive rehabilitation program of 2 hours daily for 6 weeks, which is significantly more than the 2 hours twice of week undertaken by our pulmonary rehabilitation program. This significantly more intensive exercise protocol could explain the marked improvement in both quality of life and mood symptoms in the study and highlights the link between physical capacity and mood. Our study showed that despite the lack of improvement in SGRQ, there was an improvement in anxiety and depression symptoms, which may indicate that these symptoms are more responsive to the effects of exercise and rehabilitation.

Our study used GAI and GDS to screen and determine improvement. This may impact the interpretation of our findings, as the clinical implications of changes in scores have not been determined. At the time of devising this study, GAI and GDS were considered to be more specific than HADS (127, 141) and were used in our hospital, therefore were chosen as outcomes in this study. More recent studies have since shown that after some alteration in HADS-D scores, it has become a more precise test (140). Added to the fact that HADS scores have now a validated MCID, HADS is the most validated test for the screening and assessing improvement of anxiety and depression in patients with chronic lung disease and may be a better option for future studies.

Effects of CBT on depression

As demonstrated in previous studies (174, 175), our study showed a significant improvement in GDS by the end of rehabilitation for both the Control and Intervention group; however, the Intervention group seemed to have a larger although modest reduction in mean GDS of 3.1 (almost 50% of baseline score) compared to the Control group (1.34) and although there was a trend it did not reach statistical significance (p = 0.053). Interestingly, there was an overall improvement in GDS in almost all patients that attended CBT, while the control group showed that approximately 2/3 of the patients improved (Figure 4). The improvement pattern in those that attended CBT was similar to changes found in GAI and SGRQ for both Intervention and Control groups. After CBT, the level of reduction of depression scores in our study was similar to the

study by Catalfo *et al.* (40) which had a more intensive rehabilitation program, which may indicate that CBT could augment the psychological benefits of pulmonary rehabilitation. A factor that could have contributed to the lack of significance between Control and Intervention groups by the end of rehabilitation was the overall improvement in all patients, which could have been secondary to the physical improvements caused by rehabilitation. Another factor that may have been relevant is the possible effects of psychological teaching during rehabilitation. However, this was modest in our rehabilitation program - entailing a 1-hour session in problem-solving, and a basic education session regarding the association of anxiety and depression with chronic lung disease (Appendix 1). The dampening effect of pulmonary rehabilitation may have been present in another recent similar study, which used 6 sessions of group-based CBT given with a similar pulmonary rehabilitation program (175). Our study had an intention-to-treat analysis that may have also had a dampening effect in assessing improvement in GDS, caused by the significant withdrawal rate in the study.

Our study showed a sustained improvement in GDS at 3 and 12 months, which did not reach significance at 3 months and 12 months follow-up. The lack of significant difference due to the reduced sample size analysed, especially at 12 months, causing a type 2 error. Another compounding effect was the intention-to-treat analysis that in a cohort with a high dropout rate could underestimate the change due to CBT. This demonstrates that CBT could have an effect in prolonging pulmonary rehabilitation benefits in patients with symptoms of depression, a fact supported by the demonstration of sustained improvement of GDS between baseline and follow-up for the Intervention group but not for the Control group.

Effects of CBT on Anxiety

With regards to anxiety symptoms, the Intervention and Control groups had very similar results with a significant improvement in the score by the end of rehabilitation that did not sustain to 3 and 12 months. The reason for the lack of sustained improvement in GAI or the discrepancy between anxiety and depression was not clear, although similar results were demonstrated in a comparable study that used mindfulness and CBT added to pulmonary rehabilitation (189). Possible reasons for the heterogeneity of results are: different methods of anxiety symptoms assessment tools (175), durations of CBT, method of delivery of therapy or if CBT was aimed at panic symptoms or generalized anxiety. There have been mixed results regarding therapy delivery and duration and improvement in anxiety and depression scores. A study by Hynninen et al. (170) showed sustained improvement in both depression and anxiety, although the study involved 7 sessions of 2 hours of group delivered CBT, which is significantly more than our protocol of 6 sessions with 2 face to face and 4 phone delivered sessions. On the other hand, a study by Farver-Vestergaard *et al.* (189) using mindfulness-based CBT provided 8 telephone sessions and 8 group sessions added to pulmonary rehabilitation and showed a reduction in depression symptoms but not anxiety. The study by Livermore *et al.* (173) which had a targeted protocol to panic-related anxiety symptoms given to post-pulmonary rehabilitation patients, showed a significant reduction in anxiety score up to 18 months post treatment, although there was no change in depression scores. This may imply that the cognitive behaviour model of panic disorders could be an important factor in the development of anxiety in patients with chronic lung disease (80). Targeted therapy (aimed at panic-related anxiety) such as: approaches that target misinterpretation of normal bodily sensation, education regarding the cycle of panic anxiety in COPD and breathing technique such as "pursed lip breathing'' (173); maybe more important than the number of sessions attended.

Different measures of anxiety may have a confounding effect when comparing different studies, as they may possess differences in sensitivity or precision in measuring changes over time. As an example, a study by Luk *et al.* (175) did not demonstrate an improvement in anxiety symptoms when using HADS but did when using the Depression Anxiety Stress Scale (DASS), indicating that tools like HADS are less

sensitive or that tools such as DASS are having a false-positive effect due to the overlap of depression symptoms and symptoms secondary to a chronic disease (134).

Effects of CBT to 6 minute walk test and pulmonary rehabilitation attendance.

We did not demonstrate an improvement in 6MWT in either Intervention or Control groups. However, there was an improvement during pulmonary rehabilitation of 58% of the patients. This is similar to previously reported results from our rehabilitation program, which showed a response rate between 56% and 58% of participants (280, 281), and is similar to other studies that have shown response between 47% and 67% of participants (231, 282). Other pulmonary rehabilitation programs with more sessions have shown greater 6MWT improvement (40, 278, 279). The study by Luk et al. (175) used a similar pulmonary rehabilitation program as our study and did not show an improvement in 6MWT for the control group, however in this study, 6 sessions of group-based CBT was associated with an improvement in 6MWT.

Symptoms of anxiety and depression correlate with reduced attendance rate at pulmonary rehabilitation programs (88, 231), and the presence of symptoms of depression is the strongest correlate to poor treatment adherence (230). As anticipated, this study showed that targeted psychological therapy with CBT was associated with improved attendance at pulmonary rehabilitation. In our cohort, the improved attendance did not translate to improved physiological markers such as 6MWT or improved SGRQ. Nevertheless, improved attendance may have had a psychological benefit to the intervention group, as pulmonary rehabilitation completion has been associated with improvement in anxiety and depression symptoms (39).

Impact of cognitive impairment

A quarter of our patients (n=13) had mild cognitive impairment based on MoCA scores. In our small subgroup analysis, these patients did not respond significantly to pulmonary rehabilitation, oppose to patients without cognitive impairment, although there was no significant difference between the groups. This finding differs from a previous larger of study by Cleutjens *et al.* (258) which showed that the presence of cognitive impairment did not impact pulmonary rehabilitation, although their program was longer and went from 8 to 14 weeks. Although the subgroup analysis is limited, and the small numbers could have caused a lack of identifiable improvement, other reasons for the discrepancy with a previous study (258) was not obvious. It is possible that patients with cognitive impairment may require a more extended rehabilitation program to demonstrate improvement in anxiety and depression symptoms and education sessions may have reduced impact on these patients. Commonly in COPD patients with cognitive impairment, there is an impairment in executive function and cognitive flexibility, areas that are essential to implement new techniques and strategies that are learnt in pulmonary rehabilitation. Consequently, an extended pulmonary rehabilitation program or the addition of other approaches, such as CBT may be beneficial. The impact of CBT among these patients is unclear, but studies have been encouraging among this group in reducing symptoms of anxiety and depression (257). Patients with cognitive impairment have shown decreased attendance rate to pulmonary rehabilitation (258); in our study, CBT improved attendance, which may be beneficial in this population with a more reduced attendance rate.

Limitations

The main limitation in our study was slower than expected enrolment and high rates of withdrawal or failure to attend therapy, leading to a relatively small number of patients completing the Intervention arm. In the Intervention arm, 10 of 24 patients (42%) withdrew or did not attend pulmonary rehabilitation and CBT. Compared to another study that had only employed telephone-based CBT (37) this is a lower than expected completion rate. 31% of patients approached to the study declined therapy before receiving any CBT, which could reflect pre-conceptions of what CBT entails and its effectiveness, or the stigma associated with psychological conditions. The addition of CBT to pulmonary rehabilitation treatment could be seen by some as cumbersome, although in general, patients that did not attend CBT also failed to attend pulmonary rehabilitation. It is possible that solely telephone-based therapy would have fewer withdrawals, which would make it a more attractive method of additional CBT therapy.

The final number of participants was approximately two-thirds of the total number originally planned, due to limited resources available, and the slower than anticipated recruitment rate (plus the high dropout rate from the Intervention group). Therefore, a decision was made to end the study at 65 randomised participants. The study did not use block randomization, and unfortunately, there was a disproportionate number of patients randomized to the Control group of the study early in the randomization process. The disproportionate number of patients randomized into the Control group and the high withdrawal rate in the Intervention group led to an unbalanced study. Follow-up results at 12 months were also restricted, due to a reduction in human resources (e.g. retirement of the research nurse involved in the study and the primary investigator moving interstate to undergo specialization training) and only the data of 41 patients were acquired. The small number of patients at 12 months would make the analysis more susceptible to type 2 error, where we would fail to demonstrate a difference when there truly was one. The high withdrawal rate could also have led to a selection bias in the study, although this was mitigated by the intention to treat analysis. CBT seems to improve depression scores, but possibly only to patients already predisposed to engage in treatment, as shown in the waterfall plot. Independent of this matter, offering CBT to patients with depression during pulmonary rehabilitation would be beneficial, even if only to those willing to participate.

The study was a pragmatic approach for all patients, independent of their underlying condition undergoing pulmonary rehabilitation. This approach was chosen based on the hypothesis that an integrated pulmonary rehabilitation program with psychological treatment would benefit all patients. Although there was no difference in between groups, it is possible that psychological comorbidities are different between pulmonary conditions and consequently require different approaches, an aspect that was not assessed in our study.

Future considerations

Improvement in depression scores in the CBT group indicates the possible benefit in adding this treatment to patients with depressive symptoms attending pulmonary rehabilitation. Patients have the opportunity to learn strategies to manage depressive symptoms like cognitive restructuring and have opportunities to practice those techniques during safe and supervised exposures that cause dyspnoea. The pulmonary rehabilitation sessions can create positive experiences, improve acceptance and has the potential for desensitization of shortness of breath. How much teaching or how many sessions are sufficient to achieve proficiency in deploying these strategies is not clear; however, more sessions are likely to improve the likelihood of success (170, 172, 174). The target of therapy could play an essential role in the improvement of anxiety symptoms, as possibly the addition of therapy more directed at panic attack related anxiety be more beneficial to those with anxiety symptoms (173). More intensive pulmonary rehabilitation programs are also likely to be more effective to improve mood symptoms (40), and in this context, the addition of CBT can lead to more opportunities to employ learnt strategies and possibly be a more effective treatment. Other options for rehabilitation such as home rehabilitation (283) are possibly as effective as usual pulmonary rehabilitation, making telephone-based CBT an ideal additional therapy for this form of rehabilitation. Another aspect that needs clarification is which method of delivery is the most efficient and cost-effective; as face-to-face may be more effective for anxiety symptoms (173), while telephone-based therapy may have better patient engagement (37).

Conclusions

In conclusion, this randomized control trial of mixed face-to-face and telephone-delivered CBT versus usual care, in patients undergoing pulmonary rehabilitation, found no difference in depression, anxiety and quality of life symptoms at the end of pulmonary rehabilitation. There was an associated sustained but modest improvement in depressions scores at 3- and 12-months follow-up in the Intervention group, which was not demonstrated in the Control group. The addition of CBT to pulmonary rehabilitation did not improve anxiety and quality of life symptoms compared to pulmonary rehabilitation alone at 3- and 12-months follow-up. The use of CBT did improve pulmonary rehabilitation attendance, although this did not translate into an improvement in psychological or physical markers. A subgroup analysis of patients with mild cognitive impairment based on reduced MoCA scores showed that the effectiveness of pulmonary rehabilitation was reduced. This study was limited by the high withdrawal rate in the intervention arm, which impaired the power of the study and may limit the clinical application of this form of CBT in this group. Overall, in this study, the use of CBT did not demonstrate a significant improvement in psychological parameters by the end of rehabilitation or at 12 months follow-up. Although suggestive for improvement in depression symptoms, this study could not demonstrate evidence for the usefulness of CBT for patients with chronic lung disease and psychological comorbidities.

Future studies should assess the effect of CBT on depression symptoms in this population with larger studies; better determine the effect of targeted therapy against panic attack related anxiety for those with anxiety symptoms and assess the difference in face-to-face therapy or telephone-based CBT in this population.

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Appendix:

Appendix 1:

<u>**BETTER BREATHING PROGRAM.**</u>

Monday 24th September to Friday 16th November 2018

Tutorial Rooms: 2 - 10.00am - 12.00pm

Week 1	**Monday**	24 Sept	Introduction/Anatomy and your lung condition **Physiotherapist**
	Friday	28 Sept	Breathlessness/How do you breathe & Exercise and its benefits/Spirometry **Physiotherapist**
Week 2	**Monday**	1 Oct	PUBLIC HOLIDAY
	Friday	5 Oct	Living with Chronic Lung Disease **Social Worker**
Week 3	**Monday**	8 Oct	Medical Management of Respiratory Conditions **Doctor**
	Friday	12 Oct	Problem Solving **Psychologist**
Week 4	**Monday**	15 Oct	Effective Use of Inhaler Devices **Clinical Nurse Consultant**
	Friday	19 Oct	Anxiety and Depression in Chronic Lung Disease

			Psychologist
Week 5	**Monday**	22 Oct	Good Eating Guide **Dietician**
	Friday	26 Oct	Speech Therapy **Speech Pathologist** (approx 45min) Community Support **Community Liaison Nurse** (approx 15min)
Week 6	**Monday**	29 Oct	Triggers and Action Plans for Flare Ups **Clinical Nurse Consultant**
	Friday	2 Nov	Staying Active – Session 1 **Occupational Therapist**
Week 7	**Monday**	5 Nov	No education session Patients to arrive at 11am for exercise
	Friday	9 Nov	Session 2: Stress Management and Relaxation **Occupational Therapist**
Week 8	**Monday**	12 Nov	Drugs and Your Condition **Pharmacist**
	Friday	16 Nov	Assessment and Program Wrap Up **Physiotherapist**