Health-related Quality of Life and its Associated Variables among Individuals with Idiopathic Pulmonary Fibrosis

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Dedication

To all of you who have experienced the pain and loss associated with idiopathic pulmonary fibrosis, and in memory of those we have lost to idiopathic pulmonary fibrosis, this is for you.

Abstract

Idiopathic pulmonary fibrosis (IPF) is a debilitating lung disease with a median survival of only three to five years from the time of diagnosis, with no known cure, or treatment to extend survival. Due to a lack of clinical studies, large gaps remain in understanding how IPF affects health-related quality of life (HRQOL). Because of the terminal nature of IPF, an improved understanding of how this disease affects patients' lives is needed. The works presented in this dissertation revealed that individuals with IPF are at greater risk for cognitive abnormalities, and confirmed that they are more likely to have depressive symptoms, and worsened HRQOL. The pathways among the variables cannot be easily elucidated, especially the co-existence of depressive symptoms and cognitive impairment. Nonetheless, the presence of depressive symptoms should not be overlooked in research or in clinical management, as depression may be associated with dyspnea, the symptom most commonly found to be responsible for the compromised HRQOL seen in IPF, and could be of increased interest if treating the depression could result in the alleviation of dyspnea and amelioration of HRQOL. The significance of the cognitive impairment observed among individuals with IPF remains unclear, both for selecting therapies and anticipating expected treatment outcomes. Further research is needed to understand if exertional hypoxia is related to the cognitive abnormalities noted in cases of severe IPF, or if there are long term benefits to correcting exertional hypoxia. Patient reported outcomes and HROQL data assist clinicians by providing insight from the patient’s perspective about the level of illness burden and the effectiveness of a given

intervention. Understanding which measures of health are most valued by patients is critical when establishing a plan of care, especially if asking patients to comply with a burdensome therapy such as ambulatory oxygen (AO). The role of AO in treating exertional hypoxia in IPF is obscure and more data are needed about its impact on disease progression, and HRQOL. Determining which variables are associated with HRQOL may facilitate clinician and patient interpretation of disease progression and the effects of therapy.

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CHAPTER 1 – INTRODUCTION

Overview

Chapter 1 provides a brief background on idiopathic pulmonary fibrosis and introduces health-related quality of life as the constant variable unifying the papers presented in this dissertation. As little is known about idiopathic pulmonary fibrosis, there is a pressing need for additional studies to investigate the unique needs of this patient population and to understand what can be done to alleviate the burdens of this very debilitating illness.

Idiopathic Pulmonary Fibrosis

Background

Interstitial lung disease (ILD) is a group of diseases that affect the lung parenchyma and presents with variable etiologies, clinical presentations, radiographic patterns, and histological appearances. The most common types of ILD are idiopathic pulmonary fibrosis (IPF), connective tissue disease-associated ILD, hypersensitivity pneumonitis, and sarcoidosis.

The different types of lung diseases that are included in the group of diseases known as ILD each have unique characteristics and presentations. The American Thoracic Society and European Respiratory Society (2000) developed a classification system that included the following seven types of ILD, each with its own diagnostic criteria: Usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia, acute interstitial pneumonia, respiratory bronchiolitis, desquamative interstitial pneumonia, and lymphocytic interstitial pneumonia (Alhamad & Cosgrove, 2011).

ILDs are characterized by restrictive patterns on pulmonary function tests, meaning that individuals with this type of lung disorder cannot expand their lungs with inhalation. In contrast, individuals with obstructive lung diseases such as chronic obstructive pulmonary disease (including emphysema), asthma, bronchiectasis, and cystic fibrosis, have difficulty fully exhaling the air from their lungs.

IPF, the most common form of ILD is characterized by progressive fibrosis of the lung parenchyma and worsening ventilatory restriction, which ultimately culminates in

respiratory failure and death. The median survival is less than three years (Swigris, Gould, & Wilson, 2005). It is estimated that in the United States, IPF affects between 130,00-200,000 individuals, resulting in 50,000 deaths per year (Raghu et al., 2006). The median age at diagnosis is 63 years of age, and the median survival is less than three years from diagnosis (Swigris, Gould, & Wilson, 2005).

The IPF diagnosis is made by the identification of the usual interstitial pneumonia (UIP) histological pattern on biopsy or by the presence of reticular abnormalities and honeycombing, especially in the bases of the lungs, seen on high resolution of computerized tomography (CT) of the chest. Pulmonary function testing will yield restricted lung volumes and a decreased diffusion capacity (DLCO). Decreased oxygen transfer and desaturation with exertion can be correlated with the extent of disease seen on the CT scan. In moderate to severe cases, pulmonary hypertension may also be present (Schunemann, 2011).

Clinical manifestations of IPF include a relentless cough with minimal to no sputum production and progressive shortness of breath present for at least three to four months. As such, dyspnea and cough are the hallmark symptoms of IPF, both of which negatively impact survival and health-related quality of life (HRQOL). In the absence of a cure, the management of IPF focuses on symptom relief, pulmonary rehabilitation, treatment of co-morbidities, lung transplantation, and other therapies aimed at improving HRQOL (Raghu et al., 2011).

Health-related Quality of Life

Health-related quality of life is a self-reported concept encompassing the dimensions of quality of life that have been shown to affect either physical or mental health to enable clinicians and researchers to scientifically measure the influence that health has on quality of life (Centers for Disease Control and Prevention, 2000). Patient reported outcomes such as HRQOL help clinicians understand illness burden and provide a way to measure treatment effect by incorporating domains, for example, such as perceived physical health, role functions, social health, spirituality, sexuality, general wellbeing, life satisfaction, and environment (Andreson & Meyers, 2000), as well as subjective perceptions of the presence and severity of symptoms of disease. Dominick et al. (2002) demonstrated that self-assessed health status can be a much stronger predictor of morbidity and mortality than many traditional objective measures.

That individuals with IPF suffer from poor HRQOL is well known. Martinez at al. (2009) specifically demonstrated that individuals with IPF had significantly compromised HRQOL both in physical and psychological functioning. They found that the extent of dyspnea experienced was the biggest influencing factor of HRQOL. De Vries, Kessels, and Drent (2001) found that the HRQOL of individuals with IPF was impaired when compared to a control group, especially in the domains of physical health and level of independence. They found that patients' perceptions of dyspnea often did not correlate with objective measures of shortness of breath. In their systematic review, Swigris et al. (2005) examined seven studies assessing HRQOL in patients with IPF. They concluded that subjective perceptions of dyspnea correlated more with HRQOL than any other marker of disease severity or symptom. The strongest association found with dyspnea

was physical health, but other domains with which it was associated included energy, fatigue, and to a lesser extent, emotional health.

The poor prognosis, severity of the illness, and the discouraging responses to intended therapies renders HRQOL of great importance in IPF. Understanding HRQOL among individuals with IPF is the unifying variable of this dissertation, present in each of the works described. While the other variables studied may differ among the chapters, they are always brought back to how they affect HRQOL, and how they can be manipulated to increase HRQL. Due to the strong association of dyspnea with HRQL, it is of particular interest how supplemental oxygen therapy affects HRQOL in the face of the patients' experience of dyspnea.

Ambulatory Oxygen

From clinical experience, it is evident that having to use ambulatory oxygen is very distressing to patients. Oxygen therapy is often resisted because of its cumbersome and impractical nature, side effects of drying out the nasal passages, and an awareness of its disagreeable cosmetic attributes (Earnest, 2002).

A hallmark characteristic of the pathophysiology of IPF is impaired gas exchange which worsens notably with exertion. This exertion-provoked widening of the alveolar arterial oxygen gradient and subsequent resulting hypoxia is thought to be secondary to multiple deficiencies including a ventilation/perfusion ratio mismatch, decreased partial pressure of oxygen in mixed venous blood, and venous admixture (Flaherty et al., 2006). This widening presents unique oxygenation challenges since individuals with IPF will

often have normal oxygen saturation (SpO2) levels during rest but require high levels of supplemental oxygen therapy with activity (exertional hypoxia).

In contrast, a state of continuous hypoxia, such as what is seen among the obstructive lung disease, may cause limited exercise capacity, cognitive function decline, dyspnea, decreased survival, and pulmonary hypertension leading to right heart failure (Flaherty et al., 2006). With the exception of improving the hypoxemic element of IPF-related pulmonary hypertension, the concept of oxygen therapy prolonging or shortening the lifespan in patients with IPF is only theoretical and based on what is known from studies investigating obstructive lung diseases, which ultimately may not be applicable for patients with IPF (Douglas, Ryu, & Schroeder, 2000).

The American Thoracic Society recommends that individuals with IPF who have resting hypoxia be treated with supplemental oxygen. This decision was made by physiologic rationale and ethical considerations over not prescribing oxygen therapy (Raghu et al., 2011). The guidelines do not address exertional hypoxia and refrain from recommending the use ambulatory oxygen (AO) for individuals who desaturate with activity but maintain a normal SpO2 at rest.

There is very little information about how the use of AO for exertional hypoxia in IPF affects HRQOL. In their study demonstrating that individuals with IPF had worse HRQOL, Martinez at al. (2009) found that their sample comprised primarily normocapnic to mildly hypoxic individuals, and they did not include oxygen use as a variable. De Vries, Kessels, and Drent (2001) noted that the HRQOL of IPF participants using supplemental oxygen therapy was not different from the HRQOL of IPF

participants not using supplemental oxygen therapy. However, they did not control for case-mix or adherence. It was also not reported how the use of oxygen therapy was defined or measured, or if they were comparing individuals with known oxygen prescriptions with individuals whose disease severity did not yet indicate a need for oxygen therapy, or whether they took into account the patients' desires to wear or not to wear supplemental oxygen. In their systematic review, Swigris et al. (2005) found that the associations between HRQOL and oxygen use were weak, but they did not comment on how oxygenation was conceptually or operationally defined, or its relationship with disease severity.

Subsequently, AO therapy is prescribed based on the favorable response seen in real-time during the six-minute walk test and an underlying assumption that it will be of benefit to these individuals. But how the correction of exertional hypoxia affects prognosis, survival, physiologic markers, or HRQOL, remains unknown. Although studying the effects of AO in IPF was deemed currently not feasible, Chapter 2 of this dissertation explores what is known about the use of AO in IPF. The chapter presents argument challenging the current practice of prescribing AO, and questions whether there is enough of a treatment effect to render its distressing nature worthwhile.

Even if the rigorous study of AO use in exertional hypoxia was feasible, there is still the concern that a non-effect would be unlikely to have an impact given the ethical implications of not prescribing oxygen (Raghu et al., 2011). This suggests that, in general, clinicians do believe in the theorized benefits of AO when used as directed. As mentioned earlier, there are many barriers to using AO as directed and they are difficult

to overcome. If the goal is to empower individuals to overcome these barriers, a study contributing to the knowledge about the benefits of AO could help break down these barriers by increasing the perceived benefit-to-harm ratio.

According to the Health Belief Model (HBM), benefits and barriers may predict behavior when the goal is to prevent a negative health outcome (Carpenter, 2010). Because no solid negative health outcomes have been directly associated with non-adherence to AO in individuals with IPF, this population of patients could be less likely to be motivated to adhere to their prescribed oxygen therapy. If it can be shown that individuals who adhere to prescribed AO are somehow benefitted, patients may be more motivated to use their supplemental oxygen as prescribed. Cognitive function was speculated to be an area where preventing hypoxic episodes could make a difference (to the benefit of patients).

Cognitive Function

Anecdotal observation from clinical experience at the Interstitial Lung Disease Clinic at the University of Minnesota Health revealed that patients with severe IPF appeared to have a difficult time grasping and recalling certain concepts pertaining to their illness and/or plan of care. Neuropsychological decline has been shown to decrease the quality of life of patients and families, and has been associated with mood disturbances, functional limitations, and increased health care expenditures (Hung et al., 2009; Sendelbach et al., 2005). Neurocognitive changes can manifest in areas such as memory, concentration, learning, and visual-motor response speeds (Sendelbach et al., 2005).

Not yet studied among the ILDs, cognitive impairment and its correlation with hypoxia has been well documented in advanced chronic obstructive pulmonary disease (COPD) (Hung et al. 2009). In COPD, cerebral perfusion has been shown to be significantly altered, with more abnormalities seen in participants requiring supplemental oxygen therapy. Abnormal brain perfusion scans have also been found to correlate with worsening neurocognitive test results, suggesting that decreased cerebral perfusion may be responsible for compromised cognitive function in areas such as a decline in verbal memory, delayed recall, and ability to pay attention (Ortapamuk & Naldoken, 2006).

Although it is by now known that hypoxemia will alter cognitive function, it is not completely clear what level of oxygenation is appropriate for proper cognitive functioning (Flaherty et al., 2006). If individuals with severe IPF have greater cognitive decline, a possible explanation warranting further study could relate to the inadequacy of the clinical management of hypoxia or participant non-adherence with recommended oxygen therapy.

The next step in this process was to first determine if, in fact, there is a correlation between disease severity, cognitive impairment, and HRQOL, among individuals with IPF. Chapter 3 of this dissertation presents the published findings of this trailblazing study.

It is well known that the diagnosis of Major Depressive Disorder has been linked to impaired memory, trouble with tasks requiring concentration, and a general decrease in cognitive function (Biringer et al., 2001). In the case of co-existing depression and cognitive dysfunction, it is often impossible to differentiate if these cognitive

abnormalities are related to actual neuropsychological impairment, or by an event characterized by depression (Richard, 2006).

Depression

To avoid having to post hoc explain if depression could be partially responsible for the hypothesized decrease in cognitive function and worsened HRQOL seen in IPF, the decision was made to include depression as a separate variable, hypothesizing that doing so would clearly remove it from the differential. As demonstrated in Chapter 2, this was not the case, as individuals with severe IPF not only had worse cognitive function and poorer HRQOL, they were also more depressed.

This somewhat unexpected finding prompted the investigation of what is known about depression and depressive symptoms in IPF. Ultimately, it was concluded that while study participants with severe IPF suffered from both decreased cognitive function and increased symptoms of depression, the depression levels observed were below the threshold for clinical significance and would not require clinical intervention, rendering it unlikely that in this cohort, depression was a leading cause of decline in cognitive function. This finding supported what DeVries et al. (2001) had previously found in that while individuals with IPF may suffer from negative thoughts and feelings, they are not, in general, clinically depressed.

The significance of depression in IPF continues to be of interest beyond simply looking at what is known about its association with cognitive decline. It has been shown that in IPF, depression is independently associated with dyspnea, the symptom most commonly identified as being responsible for the worsened HRQOL (Lee et al., 2014;

Nishiyama et al., 2005). But despite this, and its independent negative impact on HRQOL, depression has not been well studied in lPF, and its under-diagnosis and undertreatment exist even among the broader chronic lung diseases (DeJean et al., 2013).

After having thoroughly reviewed the literature, a manuscript (Chapter 4 of this dissertation) was written to present what is known about HRQOL, cognitive function, and depression, among individuals with IPF. It also served as the foundation to develop an intervention-based study as a follow-up to the original study investigating cognitive function and HRQOL among individuals with IPF.

Any doubts about individuals with IPF being more likely to have poor cognitive function, experience depressive symptoms, and have worse HRQOL, have by now been dispelled, and the time came to start looking at what can be done to improve HRQOL in this patient population. Cognitive Behavior Therapy is one approach that was deemed to have promise to improve HRQOL for persons with IPF.

Cognitive Behavior Therapy

Cognitive Behavioral Therapy (CBT) is an umbrella term used for various cognitive and behavioral treatment approaches conducted by an individual specialized in its delivery. The goal of CBT is to modify maladaptive patterns of thought, feelings, and behaviors using the principle that the way that individuals perceive and process reality influences how they feel and behave. CBT employs systematic goal-oriented steps to address identified dysfunctional emotions, behaviors, and cognitive processes that may create a pathway for depression, and to replace these negative thoughts with positive ones

(Simon, 2014). The specific goals of CBT vary depending on the individual, but examples include coping, medication adherence, or problem solving.

In IPF, executive function, and to a lesser extent, visuospatial skills, psychomotor functioning, and short-term memory, are the domains that are most likely to be affected by cognitive impairment (Bors et al., 2015). Executive function demands frontostriatal-limbic integrity and is responsible for "higher" functions such as problem solving and succeeding in adhering to complex medical treatment plans. It is also the domain most likely to predict treatment response. Intact executive function is necessary in order to get the most benefit out of therapies such as CBT; if executive function is compromised, the ultimate effectiveness of CBT will be limited (Alexopoulos, 2008). However, it is interesting to note that it is among individuals with impaired executive function that the greatest impact of CBT is seen if it is targeted to improve executive function, such as problem solving, rather than an area already requiring intact executive function, such as medication adherence or self-care (Alexopolous et al., 2008). As it is individuals with impaired executive function who will most benefit from CBT, CBT could be a promising intervention for individuals with IPF.

To better understand the role of CBT as part of the treatment plan in IPF, a pilot study was developed to evaluate the impact of CBT on HRQOL in patients with IPF, and to determine the feasibility of conducting similar research on a larger scale. It was hypothesized that CBT will have a favorable effect on participants' HRQOL and symptoms related to dyspnea, fatigue, anxiety, and depression. Although it is not within the scope of this study to define how HRQOL, depression, or cognitive function,

influence one another, if the results of the study favor the use of CBT in its cohort of individuals with IPF, a second, larger study would follow with multiple exploratory analyses to further understand the stratification of disease severity, and CBT-targeted domains.

Data collection for this study ended in October of 2018. The data are currently being prepared for statistical analyses and preliminary results are anticipated in the early Fall of 2019. The rationale for this study and its methodology, are presented in Chapter 5 of this dissertation.

Conclusion

The steep stepwise decline in physical health seen in IPF is exhausting and the lack of effective treatments renders it challenging to both patients and clinicians. If the possibility exists to improve HRQOL by alleviating dyspnea from treating depressive symptoms and/or from targeting cognitive decline (executive function), then any effort towards a definitive discovery and future recommendations is well worth the endeavor.

CHAPTER 2 – AMBULATORY OXYGEN IN IPF

Overview

Chapter 2 presents a manuscript that addresses what is known about the oxygenation needs of individuals with idiopathic pulmonary fibrosis, and the implications of ambulatory oxygen use. This manuscript will be submitted for publication.

Wanted: Studies Investigating the Use of Ambulatory Oxygen for Exertional Desaturation in Idiopathic Pulmonary Fibrosis

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Word count: 1933

Wanted: Clinical Studies Investigating the Use of Ambulatory Oxygen for Exertional Desaturation in Idiopathic Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is characterized by progressive fibrosis of the lung parenchyma and worsening ventilatory restriction, which ultimately culminates in respiratory failure and death. It is estimated that in the United States, IPF affects between 130,00-200,000 individuals, and results is 50,000 deaths per year (Raghu et al., 2006). The median age of diagnosis is 63 years of age, and the median survival is less than three years from diagnosis (Swigris et al., 2005).

The IPF diagnosis is made by the identification of the usual interstitial pneumonia histological pattern on biopsy when other causes for fibrosis are absent, or by clinical criteria. Clinical manifestations of IPF include a relentless cough with minimal to no sputum production and progressive shortness of breath present for at least three to four months. In moderate to severe cases, pulmonary hypertension may also be present.

A high-resolution computerized tomography (CT) scan will reveal reticular abnormalities and honeycombing, especially in the bases of the lungs (Swigris et al., 2005). Pulmonary function testing will yield restricted lung volumes and a decreased diffusion capacity. Decreased oxygen transfer and desaturation with exertion can be correlated to the extent of disease seen on the CT scan.

Until recently, no single or combined agent had been found beneficial for the treatment of IPF. In May of 2014, the results of two separate pharmaceutical studies were

published to show that pharmaceutical agents nintedanib and pirfenidone aid in the slowing of disease progression as compared to a placebo. Although promising, the resulting decline in disease progression is minimal and neither agent is without adverse effects (King et al., 2014; Richeldi et al., 2014).

Current management of IPF focuses on symptom relief, advocating for fitness, proper nutrition, the use of supplemental oxygen, and treatment of co-morbidities. When appropriate, eligible candidates may be referred for lung transplantation. Due to the limited treatment options available, HRQOL remains a primary focus for IPF management.

Exertional Hypoxia in IPF

A hallmark characteristic of the pathophysiology of IPF is impaired gas exchange that worsens notably with exertion. The exertion-provoked widening of the alveolar arterial oxygen gradient and subsequently resulting hypoxia is thought to be secondary to multiple physiological deficiencies including a ventilation/perfusion ratio mismatch, decreased partial pressure of oxygen in mixed venous blood, and venous admixture (Flaherty et al., 2006). This phenomenon presents unique oxygenation challenges as patients with IPF may exhibit normal levels of oxygen saturation (SpO2) at rest, but requires high levels of supplemental oxygen therapy to maintain the same, or similar, levels of SpO2 with activity (exertional hypoxia).

A state of continuous hypoxia, as seen more commonly in obstructive lung disease, may cause, or worsen, pulmonary hypertension leading to right heart failure. This type of chronic hypoxia also places individuals at increased risk for limited exercise

capacity, cognitive function decline, dyspnea, and decreased survival (Flahertyet al., 2006). Alternately, the long-term significance of exertion-induced desaturations (SpO2 <88%), that are intermittent with recovery to baseline (normal) SpO2 with rest, and in the absence of resting desaturations, such as those seen in IPF, remains unknown.

Ambulatory Oxygen with Activity

Assessing exertional hypoxemia and functional capacity in patients with IPF continues to remain a clinical challenge. The American Thoracic Society recommends the six-minute walk test (6MWT) as an easy to administer test to assess functional capacity, but registry data and anecdotal clinical experience suggests that exercise testing, such as the 6MWT is seldom used when assessing patients with IPF (American Thoracic Society, 2002; Maple et al., 1996). Poor performance on the 6MWT, such as a shortened total distance walked, or inability to maintain SpO2, has been associated with increased mortality, although not independent from disease severity (Lama et al., 2003).

In the setting of continuous hypoxia, ambulatory oxygen therapy (AO) has been shown to reduce mortality, improve self-reported sleep quality, increase exercise tolerance, reduce pulmonary hypertension, and improve cognitive function (Harris-Eze et al., 1996). In a controlled clinical environment, exertionally hypoxic IPF patients experience significant improvement in exercise duration and work rate when using supplemental oxygen (Harris-Eze et al., 1996). But how AO affects survival, disease severity, or HRQOL, remains unknown.

Admittedly, based on very limited evidence, the American Thoracic Society recommends that IPF individuals with resting hypoxia be treated with AO (Raghu et al.,

2011). The recommendation is based on physiologic rationale, ethical considerations over not prescribing oxygen therapy for patients who are clinically hypoxic at rest, and data extrapolated from studies investigating AO among individuals with obstructive lung disease. Possibly due to the lack of evidence supporting the use of AO among individuals who are normocapnic at rest, no recommendation is made regarding the use of oxygen therapy among IPF individuals who are only hypoxic with activity. Nonetheless, as activity-induced desaturation can be corrected on the 6MWT with the use of supplemental oxygen, a generally accepted practice has been to advocate the use of AO in exertional hypoxia as a means to enable and encourage patients to remain physically active.

Being physically active has many benefits and plays an integral part in the prevention and treatment of chronic illnesses (Warren et al., 2010). Physical function has been shown to predict future health-related events including disability, hospitalization, and mortality (Studenski et al., 2011). In patients with COPD, a rigorous exercise program has even shown to significantly improve exercise tolerance (Casaburi et al., 1991). Individuals in all walks of life are encouraged to lead active lives, and those with IPF are not exceptions, even if it means having to use high liter flows of AO.

Health-related Quality of Life

Health-related quality of life (HRQOL) is a self-reported concept encompassing the dimensions of quality of life that affect either physical and/or mental health. It enables clinicians and researchers to scientifically measure the influence that health has on quality of life, and to establish a degree of illness burden (Centers for Disease Control

and Prevention, 2000). It also provides a non-clinical alternative to measure treatment effect by incorporating multiple domains and utilizing patient-reported outcomes (Adresen & Meyers, 2000). In some ways, self-assessed health status can be a much stronger predictor of morbidity and mortality than many traditional objective measures (Dominick et al., 2002).

Individuals with IPF have significantly compromised HRQOL, both in physical and psychological functioning. Additionally, the variable most often identified as the biggest influencing factor of HRQOL for patients with IPF is dyspnea, and it is not uncommon for patients' perceptions of how dyspneic they are to not correlate with objective measures of shortness of breath or lung function (Swigris et al., 2005; Martinez et al., 2009; De Vries et al., 2001).

In IPF, AO is prescribed based on the assumption that the favorable response to AO seen during a 6MWT in a controlled clinical environment, is reproducible in day-to-day living, ultimately benefiting that individual. But this assumption fails to acknowledge that in order to reap these benefits, individuals are asked to perform a very unpleasant intervention, and its execution requires many complex barriers to be overcome. Examples of such barriers include the weight and cumbersome nature of oxygen equipment, the cost of supplies and monthly deliveries, physical side-effects such as nosebleeds and dryness of the nasal passages, fear related to misconceptions such as dependence on supplemental oxygen, stigma and embarrassment of being identified as an individual with an illness, and the esthetically unappealing nature of the oxygen tubing (Earnest, 2002).

In actuality, the relationship between AO and HRQOL remains a mystery with results varying widely among studies. While limited data does suggest that individuals on AO have worse HRQOL, assessing AO while controlling for disease severity is challenging at best and thus its independent effect on HRQOL remains unknown (Swigris et al., 2010).

Health Belief Model

Understanding the relationship between AO and outcome variables such as HRQOL or physical activity can help elucidate how to support patients for the successful management of their oxygenation requirements. According to the Health Belief Model (HBM), individuals are more likely to engage in a health-promoting behavior if the perceived threat of a condition resulting from not engaging in the health-promoting behavior is great, and if the perceived benefit of the health-promoting behavior is also great (Carpenter, 2010).

The HBM was developed to explain which health beliefs should be targeted in public campaigns to promote positive health behaviors based on individual perceptions. It proposes that individuals are more likely to engage in a health-promoting behavior if the perceived threat of a condition resulting from not engaging in the health-promoting behavior is great, and if the perceived benefit of the health-promoting behavior is also great (Carpenter, 2010). Individuals are also more likely to engage in a targeted behavior if they perceive themselves as particularly susceptible to a given threat, and perceive the targeted behavior as having strong positive benefits that outweigh its barriers. The HBM recognizes that individuals' subjective perceptions of their susceptibility to a threat are of

greater importance to successfully adopting a health-promoting behavior than their actual susceptibility based on medical or objective data (Becker & Maiman, 1975). In other words, a change in behavior will be unlikely without participant (and in this case, clinician) buy-in.

The HBM framework proposes that individuals with IPF are more likely to use AO if they perceive the threat of desaturating as great, and if they perceive the benefits associated with AO use as greater than its associated barriers (see Figure 2.1). Adherence to AO has been

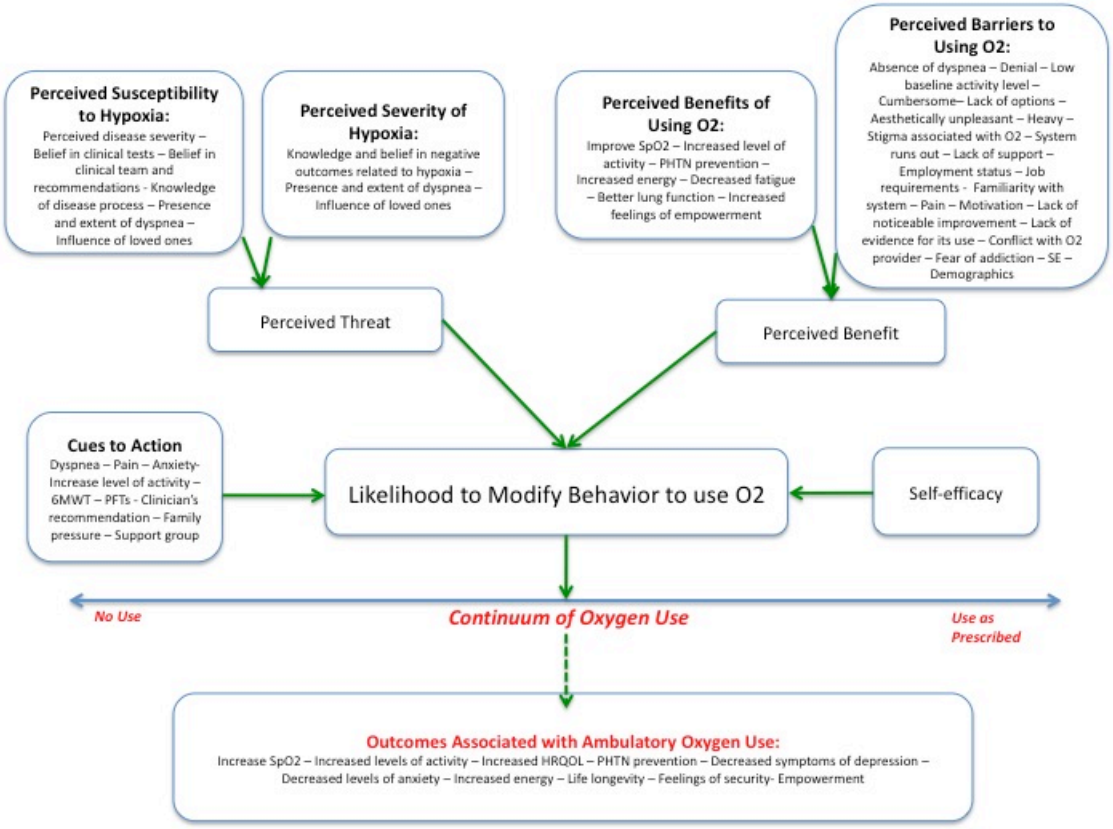

Figure 2.1. Application of the Health Belief Model to study ambulatory oxygen among individuals with IPF.

described as something that is not fixed, but that is changing continuously based perceived disease severity and need for oxygen. Among individuals with obstructive lung disease, lack of a perceived benefit from oxygen therapy has been shown to be a barrier for its use and that individuals who notice an immediate benefit, such as the alleviation of dyspnea, are more likely to use AO (Earnest, 2002). In IPF, it is not uncommon for exertionally-hypoxic individuals to, over time, acclimate to lower oxygen saturation levels and be unaware of how low their oxygen levels truly get, which according to the HBM, places them at greater risk to erroneously perceive the threat of hypoxia as low. Ironically, the lack of evidence to support the threat posed by intermittent desaturations begs the question: What is the real misconception?

Next Steps

To date, there is no recommendation for prescribing supplemental home oxygen for patients with IPF that are intermittently hypoxic with exertion. No published studies have looked at the benefits of AO in this population, either in terms of survival, physiological markers, or HRQOL. In fact, use of AO has been shown to have no dyspnea-related benefits at all among individuals with IPF who are only hypoxic with activity (Nishiyama, 2013). Despite this, AO continues to be prescribed without any published guidelines or statements of consensus. The demonstration of positive outcomes related to AO use may additionally serve to increase the perceived benefits of AO use and ultimately facilitate adherence to AO therapy.

The assumption that individuals who exhibit exertional hypoxia in a clinical setting also desaturate to that same extent in daily living remains an assumption. If individuals in fact adapt their level of activity in order to avoid the use of AO (Earnest, 2002), it may be that in daily living they do not drop their SpO2 to the extent they do during the 6MWT. Alternatively, if the 6MWT is an under-representation of physical activity, individuals may require more oxygen than what is captured during those six-minutes.

More studies are needed to determine the validity of the hypothesis that among IPF individuals with activity-induced desaturations, that those who use AO benefit by being able to remain active for longer than those who do not use AO, and subsequently have greater HRQOL. And alternately, to refute the hypothesis that AO inhibits physical activity by negatively impacting individuals' perceived level of disability, overwhelming them with barriers, and unwittingly yielding them into a "couch potato" lifestyle. But if the latter cannot be disproved, it certainly merits further evaluation of how adopting a sedentary lifestyle in order to prevent exertional desaturation compares to remaining active in the setting of exertional desaturation. The steep stepwise decline in physical health seen in IPF is exhausting and the lack of effective treatments renders it challenging to both patients and clinicians. Understanding the complex nature of AO and its interaction with HRQOL can help make a difference in the life of someone with a very unfortunate and grim diagnosis.

CHAPTER 3 – COGNITIVE FUNCTION IN IPF

Overview

Chapter 3 presents a manuscript detailing the study that investigated cognitive function among individuals with idiopathic pulmonary fibrosis. Specifically, the study was designed to determine whether individuals with severe IPF have cognitive deficits when compared to individuals who have healthy lungs. It was published in Chronic Respiratory Disease in October of 2015 (see Appendix, or visit https://us.sagepub.com/en-us/nam/journal-author-archiving-policies-and-re-use, for SAGE Publications' guidelines for including printed contributions in a dissertation or thesis).

Bors, M., Tomic, R., Perlman, D., Kim, H.J., & Whelan, T.P. (2015). Cognitive function in idiopathic pulmonary fibrosis. *Chronic Respiratory Disease 12*(4), 365-372.

Summary

Objective: The purpose of this study was to investigate if there is evidence that individuals with severe IPF have cognitive deficits when compared to individuals with healthy lungs.

Methods: Participants completed 5 neuropsychological tests: Trail Making Test (TMT) A and B, Stroop Color Word test (1,2,3), Hopkins Verbal Learning Test (HVLT), Boston Naming Test (BNT), and Grooved Pegboard, additionally, the SF-36, and Beck Depression Index.

Results: Twelve participants (7 male, mean age 69.3, 9.4 yrs) comprised the severe IPF group defined by a diffusion capacity for carbon monoxide (DLCO) < 30%. Thirty-four patients (22 male, mean age 63.2, 9.6 yrs) comprised the mild to moderate group with a DLCO > 30%. . Participating spouses (n=15, 4 male) served as the control group and had a mean age of 66.0, 10.8 yrs. Controlling for gender and age, the severe group had a significantly longer mean TMT B time (69.4, 135.9 sec) than the mild group and the control group (86.7 sec. vs. 83.2 sec.; $\rho = .004$ and .008 respectively), suggesting inferior performance on tasks requiring speed divided attention. In addition, the severe group had a significantly lower number of correctly identified colors on the Stroop 3 (22.4 vs. 30.6 vs. 38.6; $\rho < .001$), suggesting slower processing speeds when requiring suppression of a familiar response.

Conclusions: Participants with severe IPF had worse cognitive function than mild IPF or control subjects. Further research is needed to explain these findings and to develop interventions tailored to address these deficits.

Cognitive Function in Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a terminal illness characterized by progressive fibrosis of the lung parenchyma and worsening ventilatory restriction. The disease course is relentless, ultimately escalating to respiratory failure, and death (Douglas et al., 2000). It is estimated that in the United States, IPF affects between 130,00-200,000 individuals, and results in 50,000 deaths per year (Raghu et al. 2006). The median age at diagnosis is 63 years of age, and the median survival is less than three years from diagnosis (Swigris et al. 2005). The diagnosis of IPF is based upon combined clinical, radiologic, and pathologic criteria as defined by the American Thoracic Society (ATS) (Raghu et al. 2011). Early clinical manifestations of IPF include dyspnea and a cough with minimal to no sputum production.

Until recently, no single or combined agent had been found beneficial for the treatment of IPF. In May of 2014, the results of two separate pharmaceutical studies were published to show that pharmaceutical agents nintedanib and pirfenidone slow the progression of the disease compared to placebo. Although promising, the resulting decline in disease progression is minimal and neither agent is without adverse effects (King et al. 2014). Therefore, current management of IPF focuses on symptom relief, pulmonary rehabilitation, treatment of co-morbidities, and lung transplantation.

There is very little information about the impact of this disease on cognitive function. From anecdotal clinical experience at a tertiary referral center, patients with severe IPF appear to have a difficult time grasping and recalling certain concepts pertaining to their illness and/or plan of care.

Although neurocognitive decline has not exclusively been studied in IPF, it has been shown in other similar illness such as COPD and heart failure (Sendelbach et al. 2011). Changes in cognitive function can manifest in areas such as memory, concentration, learning, and visual-motor response speeds[10]. Cognitive decline may further decrease quality of life of patients and families and is associated with mood disturbances, functional limitations, and increased health care expenditures (Hung et al, 2009). This phenomenon poses a clinical challenge as these patients may require closer management and increased resource utilization in between clinic visits. In addition, it can hinder patient comprehension of information given by clinicians and negatively impact patients's compliance with recommended therapies and self-care.

The purpose of this study was to investigate if there is evidence to suggest that individuals with severe IPF have cognitive deficits. The correlation between the extent of cognitive impairment and disease severity or oxygen dependence in advanced COPD has been well documented across multiple studies (Sendelbach et al. 2005). It has been found that cerebral perfusion in COPD patients is significantly altered, with more abnormalities seen in participants requiring supplemental oxygen therapy. A correlation may be seen between the brain perfusion scans and neurocognitive test results, suggesting that decreased perfusion may be responsible for the decline in verbal memory, delayed recall, and ability to pay attention (Ortapamuk & Naldoken, 2006). Such results imply that as COPD progresses, it may bring about, or even increase abnormalities in cognitive function. If this trajectory is also true in IPF, health care professionals caring for these

individuals should be conscious of their increased risk for cognitive deficits and plan accordingly to manage their care.

Methods

This study was a prospective, cross-sectional, descriptive study. After obtaining approval from the Institutional Review Board at the University of Minnesota, patients with an IPF diagnosis were identified from the University of Minnesota Health's ILD program clinical database and were approached to determine interest in participating. Each consecutive patient with IPF who presented for a clinic visit (either new or as a follow-up) was asked to participate in the study. For patients who agreed to participate, their spouses were also asked to participate to make up a control group that would be demographically matched to the IPF participants.

Inclusion criteria for the IPF groups included a well documented diagnosis of IPF per the 2000 ATS guidelines. Exclusion criteria for all groups included a history of brain trauma including a history of cerebral vascular accident or recent concussion (in the past year); known diagnosis of a neurologic condition that affects cognition; participant's native language was not English (study materials are not available in foreign languages); and/or participant was color-blind as the Stoop Color Word Test's results would be affected by this condition. To better reflect individuals living with IPF, participants were not excluded based on co-morbidities known to affect oxygenation such as pulmonary hypertension and/or sleep apnea.

After participants consented, baseline demographic and clinical data including six-minute walk distance, spirometry, DLCO, echocardiogram, and CT scan imaging

were obtained. Eligible participants were asked to complete the following previously validated cognitive function tests: Trail Making Test A and B, the Stroop Color Word Test, the Hopkins Verbal Learning Test Revised, the Boston Naming Test, the Grooved Pegboard, and the Health Quality of Life Short Form 36 questionnaire. The Beck Depression Index-II was used to assess depression because it has been associated with both subjective complaints of cognitive dysfunction and decreased performance on objective neuropsychological testing (Richard, 2006). Testing was performed in a quiet area free from without outside disturbances. Participants completed all testing in approximately one hour. Two study personnel supervised the test: one administered the tests and other was keeping time.

Participants were stratified based on the % of predicted DLCO. This decision was based in-part on the clinical observation that at the University of Minnesota Health, IPF patients had a greater level of variance in their DLCO than in their FVC. Additionally, there is evidence to suggest that using the DLCO as an indicator was more likely to correspond with supplement oxygen requirements (Knower et al. 2001). Therefore, study subjects were a priori stratified into three groups based upon the DLCO enrollment criteria of several clinical trials that were recruiting participants at that time: control (no evidence of IPF or known condition which affects cognitive function), mild-to-moderate IPF (DLCO > 30%), and severe IPF (DLCO < 30%). The primary outcome was the Trail Making Exercise part B to detect a difference of 1 SD in mean test scores between the severe IPF patients and the controls using two-sample t-test, a sample size of 27 per group would yield a power of 0.910. Since there are multiple comparisons in this

protocol, the type 1 error alpha was set up to be 0.025 in the above mentioned power analysis.

Trail Making Test (TMT) A and B. Test takers must draw pencil lines to connect, in numerical order, 25 encircled numbers randomly arranged on a page (Part A), and 25 encircled numbers and letters in alternating order (Part B). These tests measure speed for attention, sequencing, mental fexibility, and visual search and motor function. Scoring is expressed in terms of the time, in seconds, required for the completion of the test, up to a maximum of five minutes.

Stroop Color Word Test. The Stroop Color Word Test measures information-processing speed, selective attention, cognitive flexibility, and executive function in terms of an individual's ability to suppress habitual response in favor of an unusual response (Spreen & Strauss, 1998). There are three components to the Stroop test, all requiring individuals to correctly identify as many objects as possible withing the time limit of 45 seconds. The first exercise requires participants to read the names of colors printed in black ink. The second exercise requires participants to name colors printed in the form of "XXXX" in red, yellow, or blue ink. The last, and most difficult, exercise contains the same words and colors as the previous two exercises, only now, participants are asked to name the color of the ink, and not read the word (for example, if the word GREEN was printed in red ink, participants would have to say "red" to answer correctly).

Hopkins Verbal Learning Test-Revised (HVLT-r). The HVLT-r consists of a 12-item word list, made up of four words from each of three well-known semantic categories. In this case, the categories were animals, precious gems, and housing. A total

recall score and a learning index are calculated. After 20 minutes, delayed recall of the word list is tested. Next, there is a yes/no recognition component from a list of 24 words, 12 authentic and 12 distracters. A discrimination index is calculated by substracting the false positives from the true positives. This test serves as a brief assessment of verbal recall and recognition (Brandt, 1991).

Boston Naming Test (BNT). Object naming is frequently used to identify specific cognitive deficits related to accessibility of lexical and semantic information (Freedman & Oscar-Berman, 1997). The BNT consists of 60 line drawings of items arranged from more recognizable (such as a pencil) to less recognizable (such as a protactor).

Grooved Pegboard. The grooved pegboard assesses motor tasks by evaluating eye-hand coordination and motor speed. Successful completion of the grooved pegboard requires sensory-motor integration and motor processing (Roy & Square-Storer, 1994). Beginning with the dominant hand, participants are timed, in seconds, as they rotate and place pegs into position on the board. The test is then repeated with the non-dominant hand.

Short-Form 36 (SF-36). Health-related quality of life (HRQOL) is an integral component for measuring the impact and progression of chronic diseases. The SF-36 is a generic, multi-purpose health status questionnaire designed to measure functioning and well-being along eight scales, each representing a different dimension of health. The eight dimensions are: physical functioning, role-physical, bodily pain, general health,

vitality, social functioning, role-emotional, and mental health (Ware, & Gande, 1998). Lower scores on the SF-36 are indicative of poorer HRQOL.

Beck Depression Inventory-II (BDI-II). The BDI-II is a widely used self-reporting measure of the intensity of depressive symptomatology consisting of 21 items. Higher scores are indicative of greater symptoms of depression. The rationale for including this test was derived from the results of previous studies, which found inverse associations between depressive symptoms and cognitive function (Biringer et al. 2001).

Statistics

For categorical variables, Fisher's exact test was used to examine if the frequency distribution is different between groups with the respective ρ values being presented. For continuous variables, two sample t-tests (to compare two groups for 6MW total distance in ft, DLCO, and FVC) or Analysis of Variance (ANOVA) F-tests (to compare three groups for the other continuous variables) were performed to evaluate whether the means were different from each other. When comparing three groups, an overall ρ value from ANOVA F test was presented. If the overall ρ value was ≤ 0.05, multiple comparisons were performed with Tukey-Kramer adjustment for the ρ values in order to assess which means differ from other means. The adjusted ρ values that are ≤ 0.05 are presented in the tables 1&2. All analyses were performed using SAS 9.1.3 (Carey, NC). Two-sided t-tests with $\rho \leq 0.05$ will denote statistical significance.

Data collection took place between November 2009 and April 2011. Of a total of 48 eligible IPF patients, 46 consented to participate. The two who declined participation did so due to lack of time. Of the 46 consented patients, 12 participants made up the

severe IPF group (26%), of whom 7 were men (see Table 3.1 for demographics and Table 3.2 for co-morbidities). Thirty-four participants (74%) made up the mild-to-moderate IPF group, of whom 22 were men. Fifteen family members (four were men) agreed to participate as the control group, thus age not was statistically different among the groups. All participants were Caucasian and long-term residents of the Midwest. Although the original intent was to keep enrolling until each group had at least 27 participants, recruiting and data collection were closed in April 2011 due to decreased participant enrollment.

Individuals with severe disease had shorter 6 minute walk distance, walking on average 500 feet less than patients in the mild-to-moderate group (<.0001) and were more likely to require supplemental oxygen therapy (0.01) (see Table 3.3 for pulmonary function test values).

The severe IPF group had a significantly higher mean TMT B time (135.9 sec, SD=69.4) than the mild-to-moderate IPF group or the control group (86.7 seconds [34.8] vs. 83.2 sec [35.4]; ρ value 0.004 and 0.008) (see Table 3.4 for cognitive function test results). After adjusting for gender and age, differences were still significant (ρ values 0.017 and 0.019 respectively). Participants with severe IPF performed more poorly on the cognitive function tests than those with mild-to-moderate IPF and the control group. The most significant differences were on measures of speed divided attention (TMT B), processing speeds requiring suppression of a familiar response (Stroop 3), psychomotor speeds (Grooved pegboard—both hands), and to a lesser extent, confrontation naming

(BNT). In all cases the findings were consistent with the severe IPF patients performing worse than the mild to moderate group and the control group.

Table 3.1
Demographics

	Severe	**Mild to Moderate**	**Control**	ρ
Sample size (*n*=61)	12	34	15	
Age	69 (52-79)	63 (43-83)	66 (49-81)	0.200
Gender - Male	7	22	4	0.045
Married	10	22	14	0.085
Level of education				0.160
Gr. 6-11	1	0	1	
HS diploma	6	13	5	
Some college	4	6	3	
College degree	1	15	8	
Smoking status				0.160
Current	0	0	1	
Former	5	19	4	
Never	7	15	10	
> 2 Alcoholic drinks/day	2	5	1	0.779

Note. Values listed for age are means with the range in parentheses. The rest of the values represent the number of participants.

Table 3.2
Co-morbidities

Positive for:	**Severe (*n=12*)**	**Mild to Moderate (*n=34*)**	**Control (*n=15*)**	ρ
CVA	1	3	2	0.850
Heart disease	5	11	2	0.280
Diabetes	1	6	2	0.890
Cancer	2	3	2	0.650
Mental Health	1	5	0	0.370

Note. Values listed represent the number of participants that identified the listed condition as part of their health history.

Table 3.3
Pulmonary Function Tests

	Severe	Mild to Moderate	Control	ρ
DLCO (% pred)	19.67 (9-30)	49.03 (33-95)	NA	0.007
FVC (% pred)	51.58 (26-68)	65.26 (31-78)	NA	<0.01
6MWD (in ft)	592 (140-1400)	1303 (300-2090)	NA	<0.01
Home O2	12 (of 12)	21(of 34)	NA	0.010

Note. Values listed for FVC, DLCO, and 6MWD are means with the range in parentheses.

Table 3.4
Results of Cognitive Function Tests, SF-36, and BDI-II

	Severe IPF			Mild-moderate IPF			Control			ρ
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*	*Mean*	*SD*	*Range*	
TMT-A, in sec.	42.3	12.9	30-67	33.5	10	18-58	33.1	9.8	20-46	0.04
TMT-B, in sec.	135.9	69.4	50-300	86.7	34.9	48-180	83.2	35.4	45-180	<0.01
Stroop 1	72	18.6	36-108	86	15	53-112	84	14.4	57-108	0.05
Stroop 2	49	18.8	28-65	59	11	37-85	63	10.1	41-84	0.02
Stroop 3	22	11.7	3-36	30	9.3	11-49	38	10.1	16-52	<0.01
HVLT, DR	7.7	2.4	3-12	7.8	2.3	3-12	9.7	1.7	7-12	0.01
BNT	52.5	5.4	41-60	55.4	3.3	46-60	56.7	2.5	53-60	0.01
Groove board[a]	109.1	63.4	66-300	74.1	18.8	48-140	74.5	17.6	57-108	<0.01
Groove board[b]	121.3	63.8	74-300	82.1	21.9	58-165	78.2	18.4	57-120	<0.01
SF-36	32	11.4	19-54	59.1	17.8	31-86	80.3	12	49-93	<0.01
BDI-II	13	7.1	3-29	7.7	7.1	0-25	5.2	5.4	0-20	<0.01

Note. TMT = Trail Making Test; HVLT, DR = Hopkins Verbal Leaning Test, Delayed Recall; BNT = Boston Naming Test; SF 36 = Short Form 36; BDI-II = Beck Depression Index II.
[a] Dominant hand.
[b] Non-dominant hand.

Discussion

The results of this study suggest that IPF participants with severe disease have worse cognitive function than those with mild to moderate disease and controls. They are also more likely to have poorer HRQOL (Figure 3.1) and symptoms of depression

(Figure 3.2). These findings support the original hypothesis that individuals with severe IPF have poorer cognitive function.

These findings also support what has previously been shown, that individuals with IPF suffer from worse HRQOL (Swigris et al. 2005). Health-related quality of life is especially important in this patient population given the lack of treatment options, poor mortality, and rapid progression of the disease.

Acknowledging that individuals with severe IPF may have worse cognitive function may help identify them as at risk for poorer self-care, the natural decision-making process of maintenance, monitoring, and management. In patients with heart failure, better self-care has been shown to increase HRQOL and self-reported health status, with neuropsychological decline being associated with poorer self-care and decreased compliance with treatment recommendations (Hjelm et al. 2015). For example, individuals suffering from impaired processing speeds and executive function may have altered symptom perception and delayed treatment-seeking behaviors while those who have impaired memory may have difficulty learning and remembering therapeutic regimes (Hajduk et al. 2013). Thus, finding ways to tailor illness management intervention to aid in their self-care practices may help increase their HRQOL.

It is well known that Major Depressive Disorder has been linked to impaired memory, trouble with tasks requiring concentration, and a general decrease in cognitive function (Biringer et al. 2001). Often it is impossible to differentiate if these cognitive abnormalities are related to actual neuropsychological impairment, or by an event characterized by depression.

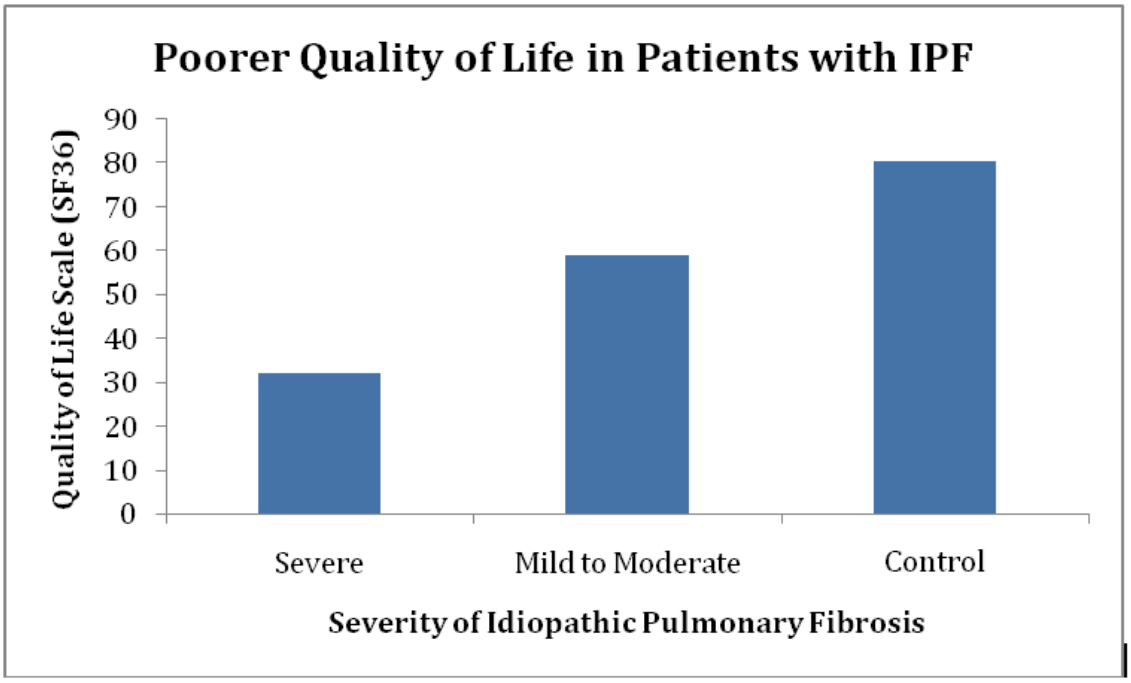

Figure 3.1.Individuals with IPF have worse quality of life.

Closer examination of the BDI-II scores revealed that of the 12 participants in the severe IPF group, one participant obtained a score of 22, indicative of moderate depression, and one participant obtained a score of 29, indicative of severe depression. All other scores ranged within the minimal or mild symptoms of depression categories. While individuals with severe IPF suffered from both decreased cognitive function and increased symptoms of depression, the depression levels observed were below the threshold for clinical significance and would not require clinical intervention. Thus, it is unlikely that depression is a leading cause of decline in cognitive function. This finding supports what DeVries et al. had previously found in that while individuals with IPF may

suffer from negative thoughts and feelings, they are not, in general, clinically depressed (De Vries et al. 2001).

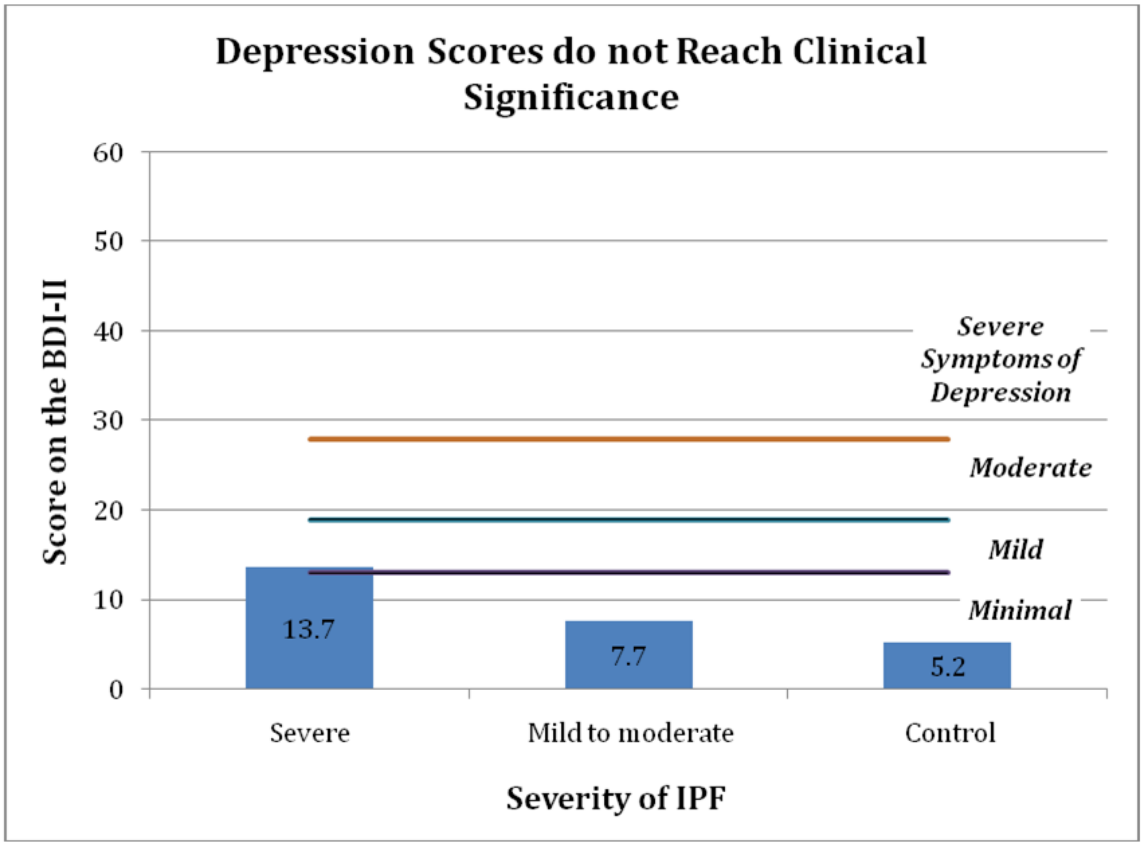

Figure 3.2 Although statistically different, depression scores were not clinically different or significant.

All patients in the group with severe IPF had been prescribed supplemental oxygen therapy based on the American Thoracic Society recommendation for IPF individuals with resting hypoxemia (Raghu et al. 2011). As expected, participants with mild-to-moderate disease required less supplement oxygen, and of the 21 participants requiring supplemental oxygen therapy in the mild-to-moderate IPF group, some needed it only with exertion while others additionally required it at rest. Due to this wide range

of supplemental oxygen requirements and the small number of participants, the impact of requiring supplemental oxygen on cognitive function was not analyzed and statistical computations were limited to addressing the differences observed between the groups as stratified by % of predicted DLCO. Although it is known that hypoxemia will alter cognitive function it is not completely clear what level of oxygenation is needed for proper cognitive function (Flaherty et al. 2006). Another possible reason for the observed decline in cognition in this patient population may be related to an inadequacy of the clinical management of hypoxemia or non-adherence with recommended supplemental oxygen therapy.

The intent of this study was not to diagnose individuals with cognitive impairment. Although screening instruments are frequently used to quantify the degree of neuropsychologic decline, cognitive impairment cannot be diagnosed by neuropsychological tools alone and requires clinical judgment. While referring patients for further assessment and/or treatment of neuropsychological changes may help provide patients and their loved ones with information and may identify a need for support, labeling individuals with a diagnosis of cognitive impairment may have psychological and psychosocial repercussions. Therefore, compared to those presenting in clinic complaining of symptoms such as impaired memory, individuals with cognitive impairment as identified by research criteria should be managed using a more conservative approach (Petersen et al. 2001).

To date, there are no Food and Drug Administration approved treatments for cognitive impairment. Studies exploring lifestyle modifications in individuals with mild

cognitive impairment recommend participation in intellectual activities, physical activities, social connectedness, and adopting a "heart healthy" diet (rich in fruits, vegetables, and omega-3 fatty acids) (Andrade, & Radhakrishan, 2009).

To better understand the implications of cognitive decline in IPF, further studies are needed to investigate how cognitive impairment affects mortality and disease progression. The strengths of this study lie in its clearly well defined cohort of IPF patients and the data obtained from multiple tests on each subject consistently demonstrating deficits across testing. These novel findings may further prove insightful in better understanding patient related outcomes and how individuals respond to therapies. The major limitations of this study include the small sample size and its homogeneity, and the unclear nature of subclinical depressive symptoms on cognition. The etiology of the observed neuropsychological impairment in this cohort of individuals with IPF remains unknown and future studies are warranted to address this matter.

Despite its limitations, this study nevertheless suggests that patients with severe IPF have poorer cognitive function, greater symptoms of depression, and worse quality of life. How individuals with IPF perceive this diagnosis is beyond the scope of this study, however, it is likely that cognitive deficits may affect patients' understanding of the disease process, treatment requirements, and ability to assume therapeutic self-care practices[10]. As patient related outcomes are increasingly identified as markers of effective therapies, it is important to acknowledge that unrecognized cognitive dysfunction may influence these outcomes. These findings expand upon the current understanding of IPF and cognitive function and suggest the need for additional, larger cohort follow up studies

examining the mechanisms involved in cognitive function and the development of interventions tailored to address these deficits

CHAPTER 4 – DEPRESSION IN IPF

Overview

Chapter 4 presents a manuscript that addresses what is known about depression among individuals with idiopathic pulmonary fibrosis, and the variables confounding the assessment of depressive symptoms such as anxiety, fatigue, disordered sleep, and cognitive decline. This manuscript has received an invitation to be submitted for publication from the Annals of the American Thoracic Society.

Understanding the Implication of Depressive Symptoms among Individuals with Idiopathic

Pulmonary Fibrosis: What Is Known

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IPF, depression, anxiety, health-related quality of life, HRQOL, dyspnea, and fatigue.

Word Count:
3874

Summary

Individuals with idiopathic pulmonary fibrosis (IPF) have poor health-related quality of life (HRQOL), often attributed to the debilitating nature of one of its hallmark symptoms, dyspnea. Given the lack of curative therapy for IPF, improving HRQOL is often the focus of therapy, leading clinicians to increasingly utilize patient reported outcomes as determinants of treatment response. Despite evidence showing that depression is independently associated with dyspnea, there is very little empirical data about the significance of depressive symptoms among individuals with IPF. The lack of guidance about the identification and management of depression, and the overlapping nature of depressive symptoms with other frequently experienced symptoms in IPF such as anxiety, fatigue, and disordered sleep, often result in its under-diagnosis and undertreatment. Yet if depression has the ability to mediate the symptom of dyspnea in IPF, insight into variables influencing depression could aid in targeting therapies and lead to improved HRQOL outcomes.

Understanding the Implication of Depressive Symptoms among Individuals with Idiopathic Pulmonary Fibrosis: What Is Known

Background

Idiopathic Pulmonary Fibrosis (IPF) is a terminal illness characterized by the relentless progression of scarring of the lung parenchyma resulting in worsening ventilatory restriction. It is the most common illness among lung diseases that affect the lung parenchyma, yet is it also the most difficult to manage, ultimately resulting in respiratory failure and death (Raghu et al. 2006). It is estimated that in the United States, IPF affects between 130,00-200,000 individuals, and results is 50,000 deaths per year (Swigris et al. 2005) . The median age at diagnosis is 63 years of age, and the median survival is less than three years from diagnosis (De Vries et al., 2001).

Dyspnea and cough are both trademark symptoms of IPF and negatively impact survival and health-related quality of life (HRQOL). Individuals with IPF have poor HRQOL that continues to worsen as the disease progresses (Lee et al. 2014). Although there is no cure, the recent addition of pharmaceutical agents nintedanib and pirfenidone is promising, even if the resulting decline in disease progression is minimal and neither agent is without adverse effects (Richeldi et al. 2014). Current management of IPF focuses on symptom relief, pulmonary rehabilitation, treatment of co-morbidities, lung transplantation, and other therapies aimed at improving HRQOL (Alhamad & Cosgrove, 2011).

Although there are no guidelines for when and how to screen for co-morbidities in IPF, the clinical impact of treating comorbidities may benefit morbidity, and has

historically focused on pathologic conditions affecting the cardiopulmonary system such as pulmonary arterial hypertension, obstructive lung disease, or cancer . Given the lack of evidence addressing the co-existence of these well-defined physiologic diseases, it comes as no surprise that there is even less information about the co-existence of symptoms related to depression. Depressive symptoms should be of particular interest as studies have shown that in IPF, depression is independently associated with dyspnea, the symptom often identified as being most responsible for lower HRQOL in IPF (Nishiyama et al., 2005). But despite this, and its independent negative impact on HRQOL and functional capacity, depression has not been well studied in IPF, and has thus been underdiagnosed and undertreated even among the broader chronic lung diseases (DeJean et al., 2013). The purpose of this paper is to present what is known about depression, and the factors associated with depression, among individuals with IPF.

Depression

While individuals suffering from depression have been shown to have altered brain activity via various types of sophisticated imaging, the origin and mechanisms of these alterations is poorly understood (Nemeroff, 2008).

The monoamine deficiency hypothesis looks at neurotransmitter imbalances and the effect of their interaction within the central nervous system when serotonin, dopamine, and norepinephrine levels are found depleted. Antidepressant agents seek to alleviate depression by, at least partially, correcting such imbalances (Nemeroff, 2008).

Another proposed theory is a hypothalamic-pituitary axis (HPA) dysregulation where abnormal levels of cortisol, in response to stress, result in depression. Depressed

individuals often have a higher level of cortisol, believed to result from an overactive HPA. This increase in adrenal corticotropic hormone is frequently referred to as dexamethasone non-suppression when the dexamethasone test is done to assess the function of the HPA, and it is considered abnormal.

Individuals with depression also have higher levels of pro-inflammatory cytokines, similar to individuals suffering from physical illness. When suffering from an illness, individuals may feel fatigued, have impaired cognitive function, and altered appetite. These symptoms can also be indicative of depression, especially if an increase in cytokines is observed in the absence of a physical illness. An increase in cytokine levels can modulate neurotransmitter levels and activate the HPA, ultimately leading to depressive symptoms (Hasler, 2010).

The complex association between depression and chronic illness is complicated by the ability of each to exacerbate the other. The lack of a clear explanation of the etiology of depression renders it difficult to treat and more research is needed to further explain the correlation between abnormal imaging, clinical presentation, and expected treatment response.

Multiple variables including age, prior history of depression, poor support system, and the severity of the underlying medical illness, can place individuals at risk for developing depressive symptoms that eventually culminate in depression. However, depression can also exist as a separate illness with unique pathophysiology, unrelated to other variables. In such cases, the pre-existing depression is burdened by the addition of the chronic illness. To better understand depressive symptoms observed among

individuals with a chronic illness such as IPF, secondary causes of depression must first be ruled out (Verma et al., 2014).

Depression, Anxiety, Fatigue, and Sleep Disorders in the Setting of Chronic Lung Disease

Depression

Depressive illness can manifest itself in many ways and may vary widely in severity and chronicity. According to the World Health Organization, depression is the leading cause of disability and is projected to be the second largest public health concern by 2020.

As a complication of chronic illness, depression affects not only the underlying disease, but also the ability to self-manage that disease, compounding to worsen that individual's level of social, occupational, and functional impairment (DeJean et al. 2013). Interestingly, individuals with chronic lung disease have been shown to have higher suicide attempt rates than individuals with non-lung related chronic conditions (Livermore et al., 2010). While the etiology of this phenomenon is not understood, it nonetheless supports what has already been shown, that illness burden is greater in lung disease than in other chronic diseases (Fiest 2011). Exactly why illness burden is greater in lung disease remains unclear, but it has been speculated to be related to the debilitating nature of dyspnea. More research is needed to clarify the role of dyspnea, and although hypoxia does not fully account for dyspnea in IPF (Nishiyama et al. 2005), to ascertain if hypoxia has a pathophyisiologic role in illness burden. In COPD, individuals who have been hospitalized have been found to be at greater risk for suicide, most notably among

women with no prior history of psychiatric illness. While still unclear, one potential explanation postulates that pre-existing depression mediates the relationship between suicidality and COPD (Young 2013). It is possible that individuals with pre-existing psychiatric conditions are more familiar with depressive symptoms and better able to manage and cope with such symptoms.

In COPD, depression can predict survival, and when managed as a separate medical comorbidity, a successful treatment response can lead to increased HRQOL (NG et al., 2007). Among individuals with COPD, depression has been linked to an increased risk of exacerbation, hospitalization, length-of-stay, physical disability, symptom burden, and fatigue. It has also been shown to be related to persistent smoking, difficulty concentrating, social withdrawal, and lethargy. Individuals with COPD who suffer from depression are at greater risk to experience poorer HRQOL, quality of sleep, appetite, reported health status, and overall functioning.

Interestingly, individuals who have undergone lung transplantation have also been found to be at greater risk for depression, even among those who did not experience depressive symptoms pre-lung transplantation (Dew 2012). Studies investigating the treatment of new-onset depressive symptoms are much needed to elucidate the extent to which the management of such symptoms also affects pulmonary-related outcome measures.

Anxiety

Four out of five individuals suffering from depression will also experience symptoms related to anxiety, the presence of excessive fear usually resulting as a

response to a specific object or set of circumstances, but in the absence of any real danger (Talwar et al., 2015). Anxiety disorders, including panic disorders, generalized anxiety disorders, and chronic anxiety, occur along a continuum ranging from normal anxiety to pathological anxiety, and it is difficult to ascertain the threshold at which anxiety begins to interfere with the daily life of an individual(Neuman et al., 2006). While it can be related to depression, anxiety is a distinct emotion that has the capacity to independently develop into being a burdensome and disabling condition.

Among individuals with COPD, anxiety is the most common predictor of poor HRQOL and functional status, and the co-existence of depression with anxiety has a greater impact on functional capacity than either physiologic markers or disease severity, and a greater impact on HRQOL than lung function (Yohannes et al., 2009). Additionally, panic disorders have been found to be 10 times greater among individuals with COPD than the general public and often result in increased symptom reporting, increased use of medical treatments, and increased rates of hospitalization (Livermore et al., 2010).

An increased risk for panic disorders has also been found among lung transplant recipients. As with depression, the increased risk for panic disorders among post-lung transplantation recipients is not related to the risk associated with panic disorders pre-transplantation, and interestingly, was not related to either acute nor chronic levels of dyspnea (Dew 2012).

Clark's Cognitive Model (*Figure 4.1*) offers a theoretical explanation for the relationship between anxiety and perceived symptom severity. Panic disorders can be

portrayed as a cyclical phenomenon that beings with something (trigger) being perceived as a threat (Yani et al., 2013). This perceived threat leads to increased apprehension, which is followed by increased awareness and body sensations, and culminates in a detrimental interpretation of these body sensations, heightening the perceived threat of the original trigger (Theander & Unosson, 2004). Thus, individuals suffering from panic disorders are more likely to focus on ambiguous physical sensations and to interpret these sensations as catastrophic.

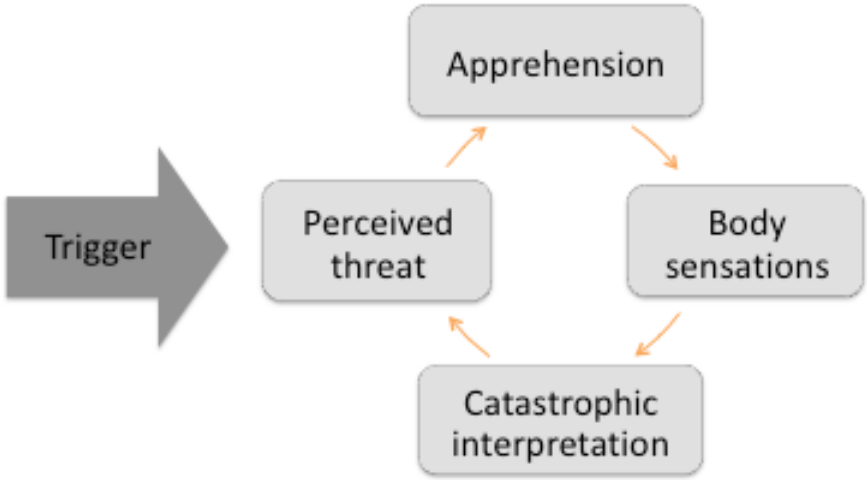

Figure 4.1. Psychopathology of Panic Disorder: Clark's Cognitive Model.
The relationship between anxiety and symptom severity is triggered by a perceived threat that renders individuals hyper-focused on their physical sensations.

These symptoms can be compounded when they overlap with somatic symptoms, such as in the case of shortness breath. If in the absence of dyspnea individuals with lung disease perceive it as a looming threat, then when they do experience shortness of breath, the result is often more catastrophic that what can be accounted for physiologically (*Figure 4.2*).

In healthy individuals, an episode of panic evokes hyperventilation with a subsequent decrease in CO2. In COPD, hyperventilation causes the lungs to hyperinflate which leads to an increased elastic load and reduced inspiratory reserves. This physiologic response increases the effort to breathe and provokes a new onset of, or exacerbates pre-existing, dyspnea (Livermore et al., 2010). Thus, treating the anxiety has the potential to alleviate the symptoms of both the panic disorder and, to some extent, the underlying lung disease.

Fatigue

Fatigue, a frequently seen symptom in lung disease, can often be vague in presentation and difficult to define. Individuals experiencing fatigue may have the same amount of fatigue even with different levels of activity or disease severity. It can lead to coping impairment, heightening its debilitating nature by leaving individuals to feel overwhelmed and unempowered (Antoniu, & Ungureanu, 2015). In COPD, fatigue has been reported to be the most frequent extra-pulmonary symptom and an independent predictor of mortality (Theander, & Unosson, 2004).

While fatigue can be related to a number of etiologies including the severity of an underlying illness, such as lung disease or depression, it can also exist coincidentally, as

an independent variable, rendering the assessment of depressive symptoms in lung disease very challenging. Among a cohort of individuals with congestive heart failure who also suffered from depression, fatigue was attributed to the congestive heart failure diagnosis, leaving the depression overlooked (Jacob et al., 2003). Similarly, clinicians working with patients with IPF should be cognizant not to miss signs of depression by attributing overlapping symptoms to the underlying lung disease.

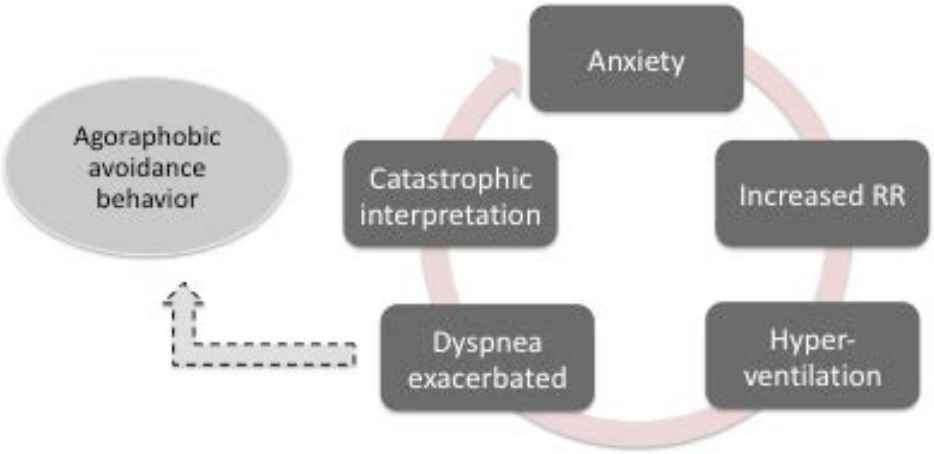

Figure 4.2. Clark's Cognitive Model Applied to Dyspnea.
In individuals with a chronic illness that is known to evoke dyspnea, Clark's Cognitive Model presents a conceptualization of how anxiety can intensify dyspnea by eliciting its cataclysmic perception.

Sleep Disorders

Sleep disturbance and depression have been shown to have a very strong association, with sleep disturbances often appearing first. The most common symptoms of sleep disturbances seen in depression include reduced sleep efficacy, impaired sleep continuity, and more frequent and longer periods of wakefulness (Nutt et al., 2008).

While antidepressants have been shown to generate significant treatment response in depression, they often fall short at addressing depression-related sleep disturbances. Although sleep abnormalities do not predict the efficacy of antidepressants in treating depression, they have been associated with poorer responses from other forms of treatment such as Cognitive Behavior Therapy (CBT). If sleep abnormalities persist even after other symptoms of depression have resolved, the risk for the recurrence of depression is significantly increased (Nutt et al., 2008).

Individuals with lung disease are at greater risk for sleep disorders such as obstructive sleep apnea, the severity of which is often measured using the apnea/hypopnea index (AHI), a value based on the number of apneic or hypopneic episodes. However, the AHI does not necessarily correlate with the subjective symptoms of obstructive sleep apnea (OSA) such as poor sleep quality and excessive daytime sleepiness, suggesting that factors contributing to sleep disturbances extend beyond respiratory events and number of arousals (Macey et al., 2010). For example, mood disturbances in particular, have been shown to be closely associated with sleep quality and sleep disturbances (Macey et al., 2010). But as depression is often classified by the severity of symptoms such as sleep disturbances, it would be challenging at best, to try to

understand the degree to which mood disorders are independent from OSA among individuals with sleep disturbances.

Depression, Dyspnea, and HRQOL

HRQOL refers to one's perceived wellbeing as affected by disease or disability over time, encompassing both physical and mental variables. Symptoms that are debilitating and disease-specific have the greatest impact on HRQOL. When dyspnea is one of the principle determinants of HRQOL, it not only significantly reduces HRQOL, but also results in mental and cognitive dysfunction, and in IPF, dyspnea is associated with both depression and functional status (Talwar et al., 2015).

Depression has been found to be an independent determinant of dyspnea (Neuman et al., 2006). Individuals with depressive symptoms who do not initially report dyspnea, have been shown to report dyspnea on subsequent measurements if depression remains a constant variable. This finding is independent of the existence, or non-existence, of an underlying physiologic explanation for the dyspnea (Kellner et al., 1992). This evidence supports the hypothesis that treating depressive symptoms among individuals with lung disease has the potential to alleviate dyspneic symptoms and thereby increase HRQOL.

Medical research has traditionally relied heavily on empiric data as the marker of disease severity and the driver behind treatment management (Marshall et all, 2006). As healthcare progresses towards an increasingly multidisciplinary approach, greater awareness is needed to understand variables that may only be apparent to the patient, such as marked shortness of breath, even if disproportionate to physiologic lung injury (Revicki et al., 2006). Patient reported outcomes (PRO) become especially relevant when

treating illnesses that have no known cure, such as IPF, where patient functioning and wellbeing become the main goal of treatment. Thus, subjective findings ought not to be dismissed by a lack of clinical markers to corroborate their existence.

Even if treating depressive symptoms can be shown to improve dyspnea, its detection remains problematic and entails an array of logistical and practical pitfalls.

Screening for Depression

The overlap of physical symptoms undeniably makes it difficult to recognize depressive symptoms as a separate illness rather than a manifestation of the underlying IPF. As a result, the threshold for screening for mental health illnesses is at risk for being higher among individuals with IPF than it is in other patient populations.

To date, there is no consensus on the best approach for screening, or for which instruments to use. While several models exist for screening depression and/or anxiety in chronic illness, many of them neglect to account for the multiple clinical and system barriers faced by clinicians. For example, the Tripartite Model of Anxiety and Depression: Psychometric Evidence and Taxonomic Implications recommend that individuals undergo an integrated assessment of general distress, physiologic hyperarousal (anxiety specific), and anhedonia (depression specific) (Wingate, & Hansen-Flaschen, 1997). It suggests a four-part approach composed of self-reported mood, clinical rating mood, self-reported symptoms, and clinical rating symptoms. It recommends that a psychiatrist work with primary care providers to identify patients who would benefit from psychiatric consultation, and that a care coordinator be designated specifically to help navigate the identified patients to ensure no one is lost in the shuffle.

Additional confusion surrounds which providers should be responsible for screening, and how often should screening be conducted. The United States Preventative Services Task Force recommends screening everyone, but only after first developing and implementing a comprehensive systematic protocol of follow-up, treatment, and monitoring (Yani et al., 2013). The Global Initiative for COPD Guidelines recommends that a detailed medical history, including the assessment of feelings of depression or anxiety, be completed at the time of diagnosis (Maurer et al., 2008).

A more cost-effective option would be the use of less complex screening tools developed to aid in the assessment of depressive symptoms. While these tools are not designed to be diagnostic, they can provide a way to look at symptom burden and can be used to support diagnostic measures (Verma et al., 2014). An ideal instrument should be tested for reliability and validity in lung disease, and have high sensitivity and specificity, an ideal instrument would also be easy to administer without being too time consuming (*see Table 4.1*).

Adding to the already identified challenges is the stigma associated with mental health illnesses, leading some individuals to conceal or downplay their symptoms of depression. Alternately, the normalization of depressive symptoms among the chronically ill also becomes a barrier as clinicians may be inclined to emphasize the link between chronic illness and depression. This unknowingly makes it harder for patients and loved ones to recognize the symptoms of depression as a separate condition that could benefit from separate and individualized treatment.

Table 4.1

Commonly Used Tools for Identifying Symptoms of Depression

Tool Name	Year	Description	# of Items	Score	Score Interpretation			
					None	Mild	Moderate	Severe
HAM-D (Hamilton Rating Scale for Depression)[a]	1960	• Measures depressive symptoms in inpatients • Emphasizes somatic symptoms over cognitive symptoms • Clinician administered • Requires some training	17	0-54	0-6	7-17	18-42	>24
BDI-II (Beck Depression Inventory)[b]	1996	• Assess symptoms seen among depressed patients • Measures somatic, behavioral, and emotional symptoms • Self-reported questionnaire	21	0-63	0-9	10-18	19-29	>29
MADRS (Montgomery-Asberg Depression Rating Scale)[c]	1979	• Severity of episodes of depression in mood disorders • Used to measure treatment response • Based on a physician assessment via clinical interview	10	0-60	0-6	7-19	20-34	>34
GDS (Geriatric Depression Scale – short form)[d]	1986	• Differentiates depression from dementia among those aged 65-85 • Questions are yes/no, based on the "past week"	15	0-15	0-4	5-8	9-11	>11
PHQ-9 (Patient Health Questionnaire)[e]	1999	• Developed to assess outpatients for depression • Self-reported questionnaire • Questions based on the "past 2 weeks"	9		0-4	5-14	15-19	>19

Notes.[a] Zigmond & Snaith (1983). [b] Dozois, Dobson & Ahnberg (1998). [c] Montgomery & Asberg (1979). [d] Sheikh & Yesavage (1986) [e] Kroenke, Spitzer, & Williams (2001).

Establishing a screening protocol requires additional resources and demands changes at the system level such instituting a taskforce to develop a plan of care trajectory ensuring patients do not "fall through the cracks". Given the limited availability of psychiatric resources in general, it is unrealistic to expect that patients flagged during screening be seen by psychiatry in a timely manner. One alternative is to hire allied health professionals to conduct additional screening and aid in triaging which patients truly need to be seen by psychiatry, or, if it would be appropriate, for some to be seen by affiliated specialties such as social work. A well-thought-out protocol should prevent duplicate work by providing accessible guidelines for common conundrums, such as if a previous referral to psychiatry precludes a patient from screening if psychiatry no longer identifies a need for follow-up. But without additional resources and an

established collaborative plan, it is unlikely that the lone act of screening will lead to improved treatment and outcomes.

Treatment

Patients with chronic lung disease identified with symptoms of depression should be considered for treatment, especially if the underlying illness is associated with functional impairment (Macey et al., 2010). However, lack of treatment options and clinician reluctance to prescribe psychotropic agents preclude many individuals from actually receiving treatment. Furthermore, many of the existing pharmaceutical agents have yet to be studied in the setting of lung disease and their harm vs. benefit ratios are poorly understood. It is also unclear what impact underlying disease severity may have on treatment response, or what constitutes as successful treatment of depression in the setting of an underlying condition that continues to progress. In such cases, a cognitive approach should not be discounted.

Cognitive Behavioral Therapy (CBT) is an umbrella term used for various cognitive and behavioral treatment approaches conducted by an individual specialized in its delivery. The goal of CBT is to modify maladaptive patterns of thought, feelings, and behaviors using the principle that how individuals perceive and process reality will influence how they feel and behave. It employs systematic goal-oriented steps to address identified dysfunctional emotions, behaviors, and cognitive processes, and to replace these negative thoughts that may create a pathway for depression, with positive ones. The specific goals of CBT vary depending on the individual, but examples include coping, medication adherence, or problem solving. Thanks to advances in fields such as tele-

medicine, CBT is now accessible to individuals whose functional limitations make it difficult for them to come to clinic (McLean et al., 2012).

Individuals with IPF: A Unique Population

Although the risk for chronic illness increases with age, the rate of depression associated with a chronic illness is not affected by age. However, the association is likely underestimated given the survival bias resulting from depressed individuals being at greater risk for making poor lifestyle choices and dying at an earlier age (Fiest, 2011). This suggests that given the advanced age at the time diagnosis, individuals with IPF may actually be at greater risk for depression than a younger person with a similar chronic illness.

Individuals with IPF have also been found to be at greater risk for sleep disorders, with conditions such REM sleep hypoventilation and obstructive sleep apnea-hypopnea syndrome remaining largely underdiagnosed (Milioli et al., 2016). In IPF, intermittent desaturations during sleep have been found to be markedly worse than desaturations noted during maximum physical exertion (Kolilekas et al., 2013). Fatigue, well-known symptom of IPF, it is often assessed and explained as manifesting from the IPF. On the other hand, excessive daytime sleepiness is not as commonly asked about, even within the context of fatigue. Assessing for daytime sleepiness could lead to a greater recognition of disordered sleep and its contributory role in fatigue. As sleep disorders have been linked with depressive symptoms, decreased HRQOL, and increased mortality, distinguishing excessive daytime sleepiness from general fatigue could help target interventions and improve outcomes.

The prevalence of depression among individuals with IPF is two-to-three times greater than among the elderly general public. Individuals with IPF who report symptoms of dyspnea are at greater risk for depression than those who do not report dyspnea. In this setting, depression becomes a persistent condition, and differs from depression seen with adjustment disorder at the time of diagnosis or following a recent exacerbation (Ryerson 2011).

Although the co-existence of depression and cognitive impairment is not uncommon, it is often not feasible to differentiate which of the two is the preceding disease. In IPF, executive function, and to a lesser extent, visuospatial skills, psychomotor functioning, and short-term memory, are the domains the most likely to be affected by cognitive impairment (Bors et al., 2015). Executive function demands frontostriatal-limbic integrity and is responsible for "higher" functions such as problem solving and succeeding in adhering to complex medical treatment plans. It is also the domain most likely to predict treatment response. Intact executive function is necessary in order to get the most benefit out of therapies such as CBT —if executive function is compromised, the ultimate effectiveness of CBT will be limited (Alexopoulos et al., 2008).

But interestingly to note, it is also among individuals with impaired executive function that the greatest impact of CBT is seen, if it is targeted to improve executive function, such as problem solving, rather than an area already requiring intact executive function, such as medication adherence or self-care (Alexopoulos et al., 2008). But as there is an increased incidence of sleep disturbances among individuals with IPF,

evaluating and treating existing sleep disturbances can help maximize the overall benefit of CBT.

Next Steps

Studies are needed to understand the relationship between lung disease and mental illness, especially in the IPF population. No study has yet evaluated the efficacy of treating depression in IPF, or if nintedanib and pirfenidone, and other anti-inflammatory agents and corticosteroids affect the trajectory of depression. It is unclear to what extent improvements in HRQOL should be expected if depressive symptoms are treated, or if efforts would be better spent directed at targeting HRQOL as a way to alleviate depressive symptoms.

Qualitative data and patient-reported outcomes (PROs) research are needed to understand the psychological impact of burdensome therapies such as long-term oxygen supplementation. While oxygen therapy improves oxygenation by correcting exertional hypoxia, it is unclear if asking individuals to comply with such an arduous intervention, despite its physiologic benefits, truly increases HRQOL, or if individuals give up activities that previously brought them joy in order to avoid its use. Incorporating PROs provides a holistic evaluation of the effectiveness of treatment interventions that includes the patient's perspective. As PROs are being used more widely as study end-points, it is important to generate supporting empirical data to better understand their significance for measures of dyspnea, depression, and HRQOL.

The steep stepwise decline in physical health seen in IPF is exhausting and the lack of effective treatments renders it challenging to both patients and clinicians. If the

possibility exists to improve HRQOL by alleviating dyspnea from treating depressive symptoms, then any effort towards a definitive discovery and future recommendations is well worth the cost.

CHAPTER 5 – COGNITIVE BEHAVIORAL THERAPY IN IPF

Overview

Chapter 5 presents the rationale behind, and the methodology of the study investigating cognitive behavioral therapy among individuals with idiopathic pulmonary fibrosis. Enrollment for the study closed in October of 2018. Data analysis is in-progress with preliminary findings expected in the fall of 2019.

Background

Cognitive Behavior Therapy has not yet been studied in IPF, and it is unclear what factors may influence its efficacy, or even its feasibility, among individuals with IPF. To better understand the role of CBT as part of the treatment plan in IPF, a pilot study was developed to evaluate the impact of CBT on HRQOL in patients with IPF, and to determine the feasibility of conducting such research on a larger scale. It was hypothesized that CBT would have a favorable effect on participants' HRQOL and symptoms related to dyspnea, fatigue, anxiety, and depression. If the results of the study favor the use of CBT in its cohort of individuals with IPF, a second, larger study will follow with multiple exploratory analyses based on the stratification of disease severity, and CBT targeted domains. Given what little is known, it was not within the scope of this study to differentiate outcome measures based on domains treated, or to identity which variable is the greatest influencer in HRQOL, disease severity, depression, cognitive function.

Specific Aims

Aim 1: To determine whether or not participating in CBT will improve the HRQOL among individuals with IPF.

Sub-aim 1a: To investigate the effectiveness of CBT in alleviating symptoms related to dyspnea, fatigue, anxiety, and depression.

Hypothesis 1: Participants' will have improved HRQOL when compared to the

control group not receiving the intervention. It is unknown to what extent the hypothesized benefits of CBT on HRQOL are related to decreased symptoms of anxiety and/or depression. Therefore, an improvement in the symptoms of dyspnea, fatigue, anxiety, and depression is also an anticipated outcome.

Aim 2: To explore the attitudes towards CBT and the experiences of individuals with IPF having received CBT.

Hypothesis 1: Due to the qualitative nature of this aim, a hypothesis has not been generated.

Aim 3: To evaluate the feasibility of conducting a larger scale CBT research among individuals with IPF.

Hypothesis 1: It is unclear how this intervention will be perceived or the burden it may impose both financially and from a practical perspective of asking individuals with a terminal illness to present to clinic more frequently than routine clinic visits. However, based on previous pharmaceutical studies also requiring frequent appointment, it is not unreasonable to hypothesize that this type of research will indeed prove feasible among individuals with IPF.

Methods

This in-part quantitative and in-part qualitative pilot study utilized a randomized cross-sectional, correlational study design. Patients with a diagnosis of IPF were identified from the University of Minnesota Health interstitial lung disease program's clinical database and approached to determine if they would be interested in participating in the clinical trial. A total of 20 individuals with IPF who agreed to participate were

randomly assign to either the CBT intervention group, or the control group who received standard medical care, and no CBT. Given that this was a pilot study, a power analysis was not completed, and the sample size kept small in order to expedite study completion and to obtain enough determine the feasibility of conducting a larger scale study.

Data Collection

Baseline demographic data as well as clinical data, to stratify disease severity, was obtained for both patients in the control and intervention groups. A 6-minute walk, spirometry, diffusion, echocardiogram, and CT scan imaging are routine tests performed as standard of care and were not ordered as part of the study protocol, but were obtained from the participants' medical record. If these studies had not been performed, they were considered missing data for the study. No additional medical testing besides what was clinically recommended was performed.

Participants were asked to complete the following battery of tests at the time of enrollment and at the completion of the CBT session (or eight-weeks post-enrollment for the control group): The Functional Assessment of Chronic Illness Therapy Fatigue Scale, the St. George Respiratory Questionnaire, The Short-Form 36, the Patient Health Questionnaire, and the Generalized Anxiety Disorder Questionnaire. If clinically indicated, a 6MWT was also completed and use to assess functional capacity. In addition, consent was obtained to contact participants in three months after study completion, at which time they were asked to repeat these tests to determine if the gains achieved through the CBT session were maintained after the sessions had ended. Participants in the control group were also asked to repeat the tests.

Qualitative data were collected at two points during the study; at the time of enrollment (prior to the first CBT session), and at the completion of the fourth, and potential final, session of CBT. This two-step approach allows for the exploration of initial attitudes towards CBT, and later, the experience of having gone through CBT.

Six-minute Walk Test (6MWT)

The American Thoracic Society (2002) recommends the six-minute walk test (6MWT) as an easy to administer test to assess functional capacity. The test is very well standardized and validated in multiple studies for patients with IPF. This test measures the distance that a patient can quickly walk on flat surface in a period of 6 minutes (the 6MWD). It evaluates the global and integrated responses of all the systems involved during exercise. During the 6MWT, patients are instructed that the objective of the test is for them to walk as far as possible in six minutes. The test was performed in a measured hallway with a qualified respiratory therapist walking alongside the patient who at the completion of the test, will record the total distance covered. Also recorded during the test were the participants' heart rates and oxygen saturation levels as measured by a portable oximeter (Brooks, Solway, & Gibbons, 2003).

Psychometric Tests

The FACIT Fatigue Scale (FACIT). The FACIT is a short, 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on 4-point scale. Higher scores represent better health (in this case, less fatigue), and lower scores represents worse health or more fatigue (Cella, Yount, Sorensen et al., 2005).

St. George's Respiratory Questionnaire (SGRQ). The St. George's Respiratory Questionnaire (SGRQ) was designed to measure impact on overall health, daily life, and perceived well-being in patients with respiratory diseases. It is made up of 50 items that are divided into three categories: Symptoms (8 items), activity (16 items), and impacts (26 items). Part 1 of the questionnaire addresses the frequency of respiratory symptoms and Part 2 addresses the patient's current state. Scores are calculated for each component as well as a total score. Higher scores indicate greater compromises in HRQOL. Although it was originally formulated and validated to measure HRQOL and dyspnea in patients with COPD and asthma, Yorke, Jones, and Swigris (2010) developed the SGRQ-I, an IPF-specific version of the SGRQ. They found that some of the items on the original tool contained weaker measurement properties when applied to patients with IPF. By removing these items and/or modifying response options, they produced and validated the SGRQ-I, which is thought to have greater sensitivity and specificity to underlying changes in IPF (Yorke, Jones, & Swigris, 2010).

Short-Form 36. Health-related quality of life is an integral component for measuring the impact and progression of chronic diseases. The Short-Form 36 (SF-36) is a generic, multi-purpose health status questionnaire designed to measure functioning and well-being along eight scales, each representing a different dimension of health. The eight dimensions are: Physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health (Ware & Gande, 1998). Items in SF-36 are able to detect positive as well as negative states of health. For each dimension, item scores are coded, summed and transformed on to a scale from 0 (worst

health) to 100 (best health). Its validity and reliability have been confirmed in numerous conditions including Chronic Obstructive Pulmonary Disease (COPD) and asthma. Most recently, it has also been shown as a valid tool for patients with IPF (Martinez, Pereira, dos Santos et al., 2009).

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report measure of anxiety and depression (Zigmond & Snaith, 1983). Each subscale contains 7 items. Patients respond on a four-point scale (0-3) for each item with higher ratings reflecting greater anxiety and depression. The subscales are internally consistent (Cronbach's alpha of .82 and .77) and demonstrate concurrent validity with other measures of depression and anxiety (Crawford et al., 2001).

The Generalized Anxiety Disorder scale (GAD-7; Spitzer et al, 2006) is a brief measure of symptoms of anxiety, based on diagnostic criteria described in DSM-IV. The GAD-7 consists of 7 questions rated on a four-point scale from "not at all" to "nearly every day." This scale demonstrates good reliability (test-retest r=.83) and procedural validity (r=.83).

The Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams, 2001) is a brief measure of symptoms of depression, based on diagnostic criteria described in DSM-IV. The PHQ-9 consists of 9 questions rated on a four-point scale from "not at all" to "nearly every day." This measure demonstrates good internal reliability (Cronbach's alpha =.89) and test-retest reliability (r=.84). Concurrent validity as measured with the SF-20 mental health scale was also strong (r=.73).

Cognitive Behavior Therapy Interventions

Participants in the CBT group attended four to six 45-minute sessions of individual psychotherapy at approximately two-week intervals. To ascertain intervention fidelity, the same psychologist trained in the delivery of CBT conducted all CBT sessions.

Each session allotted of portion of the time to focus on one of the following four areas: Psycho-education, stress management skills, problem solving, and implementation of healthy habits. The rest of the time was spent in developing rapport, application of the content material to the participant's personal life, and addressing other psychological, social or environmental issues, specific to that participant, that may impact his or her successful personal application of the CBT. To broadly define the intervention and achieve intervention fidelity, the first four sessions for each participant were structured the same way.

Breakdown of CBT Sessions

The first session focused on psycho-education about anxiety and the stress response system, including the physiologic effect of stress on the body and its impact on breathing. The rest of the session would then focus on how that participant coped with anxiety. Participants applied the CBT principles to their own experiences by identifying the stressors in their life; how these stressors affect them in physical, behavioral, psychological, social, and cognitive ways; and how they cope with these stressors. Participants worked on the recognition of both healthy and unhealthy coping.

The second session focused on developing skills to better manage stress response. Participants would be instructed on several tools, including calm breathing, progressive

muscle relaxation, mindfulness meditation, exercise, and incorporating true breaks into daily routines. Participants were equipped with specific training and resources for implementing these techniques and would leave the session with a plan for to successfully implement of one or more of these stress management skills.

The third session focused on improving problem solving skills. Participants were asked to explore their thought processes when encountering a stressful situation and to identify unhealthy thought patterns such as catastrophic thinking, unrealistic expectations, perfectionism, and/or avoidance. Participants were engaged to discover ways to develop habits by employing healthier thought and action patterns including identifying stressors, thinking realistically and directly about challenges, using self-talk to improve problem solving, and taking action to either alter a stressor or alter their responses to the stressor.

The fourth session focused on methods of identifying and implementing healthy habits to reduce stress and to overall improve their health. Healthy habits included successful stress management and problem-solving skills. When appropriate, adherence to treatment could also be incorporated as a type of healthy habit. Key areas of healthy habit formation that were addressed included the identification of realistic (short term and long term) goals, building-off of existing habits to maintain changes, employing simple and measurable changes, using visual and behavioral cues, and rewarding successes.

Although it was anticipated that most participants would likely complete the CBT these four sessions, the study was designed with the flexibility to accommodate up to a total of six sessions per participant, if at the end of the four sessions, extra attention was

indication to meet any of the identified focus area goals. Six-to-eight weeks post CBT-completion, participants returned for a booster session to assess current functioning and if needed, to reinforce the maintenance of gains made during the main phase of treatment.

Statistical Analysis

The main analyses will be by intention to treat to reduce bias due to differential attrition from the intervention and control groups. We will express continuous variable as mean +/- standard deviation and comparisons will be performed with student t-test. Within-group differences will be tested using paired-sample t-tests with post-intervention group comparisons measured using independent sample t-test. Finally, an analysis of covariance (ANCOVA) will be used to correct for imbalances between the treatment and control groups at baseline. The covariates in this analysis include baseline scores, age, sex and smoking. A P value <0.05 will be considered statistically significant. All raw scores also will be transformed into interval measures ranging from 0 to 100 using a probabilistic logistic regression model (i.e., Rasch measurement model). The purpose of this transformation is to create an interval metric to increase the accuracy of between groups comparison.

Content analysis will be used to determine themes found within the qualitative interview data. The correspondence of qualitative themes and quantitative data will be textually described.

Enrollment for this study closed in October of 2018. The data are currently being prepared for statistical analyses and preliminary results are anticipated in the early Fall of 2019.

CHAPTER 6 – SYNTHESIS

Overview

Chapter 6 presents a synthesis of the content presented in the previous chapters, its implications for nursing practice, and to make future recommendations.

Synthesis

With a median survival rate of three years, Idiopathic Pulmonary Fibrosis (IPF) is characterized by the progressive fibrosis of the lung parenchyma and worsening ventilatory restriction, ultimately culminating in respiratory failure and death (Swigris, Gould & Wilson, 2005). With limited options to halt or slow disease progression, IPF management of individuals not eligible for lung transplantation focuses primarily on the treatment of co-morbidities, symptom relief, the use of supplemental oxygen, and improving HRQOL.

This dissertation was the first to show that individuals with IPF have worse cognitive function. Neuropsychological decline has been shown to decrease the quality of life of patients and families, and has been associated with mood disturbances, functional limitations, and increased health care expenditures (Hung et al., 2009; Sendelbach et al., 2005). If it can be shown that individuals with IPF suffer from decreased cognitive function, nursing and medical interventions can be tailored to aim at decreasing attention demands, thereby supporting the individual's attentional processes and functioning.

The impact of the cognitive deficits observed is unclear. Comparative studies are needed to identify the impact of cognitive function on IPF disease trajectory and if that trajectory is susceptible to interventions aimed at either regaining cognitive function or halting the progression of decline. It is also unknown if cognitive decline is predictive of mortality independent of disease severity.

The inability to control for depression confounded the overall findings and elucidated that very little is known about depression among individuals with IPF.

Although the difference in lung function between the participants in the severe IPF group and those in the mild-moderate group was far greater than difference seen in the severity of the depressive symptoms, it is unknown at what threshold of severity, for either lung function or depressive symptoms, does cognitive decline begin to appear. Since the levels of depression observed were below the threshold of clinical significance, it is plausible to speculate that the much greater difference observed in lung function is the likely culprit. However, the possibility that cognitive function is more sensitive to depression cannot be discounted.

As individuals in the mild-moderated group showed no evidence of cognitive decline or symptoms of depression, longitudinal studies are needed to capture at what point in the trajectory of IPF do cognitive abnormalities, and/or depressive symptoms, begin to appear, and how do those changes behave as the disease progresses. Furthermore, disease severity and depression were treated as categorical variables, whereas the results of the psychometric tests were linear variables. While this is unlikely to have significantly impacted the findings given the small sample size, in a larger study, including a linear analysis of disease severity may provide information to support, or dispute, how IPF disease severity should be defined.

That individuals in the severe group had greater levels of depressive symptoms was also significant in that depression has been found to be an independent determinant for dyspnea, the symptom most commonly identified as responsible for the worsened HRQOL seen in IPF (Neuman et al., 2006). Additionally, individuals with IPF who report symptoms of dyspnea are at greater risk for depression than those who do not

report dyspnea (Ryerson et al. 2011). In this setting, depression becomes a persistent condition, and differs from depression seen with adjustment disorder at the time of diagnosis, or what might be expected following a recent exacerbation.

It is well known that individuals with IPF have worse HRQOL. It is also well known that they experience dyspnea, and that dyspnea is a very debilitating symptom, and will worsen HRQOL (Nishiyama et al. 2013). Although this could explain why illness burden is greater in lung disease than in other chronic diseases, dyspnea and clinical markers of disease severity do not always correlate, suggesting that a variable different from lung function may be responsible (Feist et al. 2011).

Individuals with depressive symptoms who do not initially report symptoms of dyspnea, have been shown to report dyspnea on subsequent measurements if depression remains a constant variable. This finding is independent of the existence, or non-existence, of an underlying physiologic explanation for the dyspnea (Kellner, Samet, & Pathak, 1992; Neuman et al., 2006). This means that the presence of inadequate lung function could be an incidental finding in someone who presents to clinic for shortness of breath. But prior to hypothesizing that treating depressive symptoms among individuals with lung disease has the potential to alleviate dyspneic symptoms and thereby increase HRQOL, additional studies are needed to better describe dyspnea as seen in depression, and if it is different than dyspnea resulting from lung disease.

The association between depression and chronic illness is complicated by the ability of each to exacerbate the other (Nemeroff, 2008). As individuals in the mild-moderate IPF group did not have depressive symptoms, it could be that the depression

seen in the severe group was related to the underlying disease severity of their lung disease. As a complication of chronic illness, depression affects not only the underlying disease, but also the ability to self-manage that disease, compounding to worsen that individual's level of social, occupational, and functional impairment (DeJean, 2013). This already grim situation is only intensified with the addition of AO.

Ambulatory oxygen is an unpleasant intervention for which there are complex barriers to overcome for which there are no tangible or practical solutions. Barriers to adherence with oxygen therapy among individuals with COPD include factors such as the weight and cumbersome nature of the oxygen equipment, physical side effects such as nosebleeds and dryness of the nasal passages, fear related to misconceptions such as dependence on supplemental oxygen, stigma and embarrassment of being identified as an individual with an illness, and the esthetically unappealing nature of the oxygen tubing (Earnest, 2002). As IPF is not a smoking-related lung disease, individuals requiring AO, who have never smoked, fear being labeled as a "smoker".

The reluctance to study oxygen use among exertionally-hypoxic individuals with IPF is inexcusable. If HRQOL is truly the focus of care, then how is it that the decision can be made that despite no evidence to support its use, the benefits of AO in someone with a rapidly progressive terminal illness, who may have cognitive impairment, and who may be depressed, outweigh its negative impact on HRQOL?

While it may seem reasonable to prescribe AO based on a documented drop in oxygen saturation observed during the 6MWT, that same phenomenon has not yet been reproduced outside of a controlled clinical environment. If individuals in fact adapt their

level of activity in order to avoid the use of AO (Earnest, 2002), it may be that in daily living they do not drop their SpO2 to the extent they do during the 6MWT. Alternatively, if the 6MWT is an under-representation of physical activity, individuals may require more oxygen than what is captured during those six-minutes.

Empirically measuring the benefits of AO in IPF poses many challenges. Although individuals are instructed on the dosage and delivery method, they are nonetheless the decision makers of whether or not to use it, when to use it, how to use, and at what liter flow. A rigorous study design would have to include a way to standardize the mode and delivery method of the AO, objectively measure its use, and account for a potential placebo effect. A very liberal approach would have been to purchase several units of a specific delivery mode of oxygen, alter half of the units to deliver room air instead of oxygen, equip all of the units with a device to track their use, ask participants to wear an actigraph monitor to correlate that the devices were used as prescribed (with activity), and ask participants to wear a portable oxygen saturation monitor that does not have a visual display to determine if the 6MWT performed in a controlled clinical environment reflects participants' activity and oxygen saturation levels at home. While some might hesitate at the ethical implications of randomizing participants who are known to desaturate into a control group utilizing dummy oxygen delivery devices that only dispense room air, an argument could be made that enrolling participants for a very short period of time, such as three days, would not cause them harm or alter their disease trajectory. A seemingly bigger concern, and what would

ultimately render this study unfeasible, was the lack of technology and complexity of the variables.

It is not the intent of dissertation to discourage the use of AO, but rather to re-evaluate the reason for recommending its use and to holistically assess patients and their readiness for complex interventions when evaluating which therapies would most benefit their HRQOL. I urge future researchers to not limit themselves by shying away from studying variables that seem confounding, difficult to measure, or that exist within a previously unidentified phenomenon.

It is my personal belief that the use of AO in extertional hypoxia among individuals with IPF is a health-promoting behavior. In part because I, as several of my colleagues, suffer from the misguided perception that its use will increase HRQOL because individuals who previously did not wear oxygen will henceforth appreciate the difference it has made in their lives, and that it will enable them to continue participating in activities they enjoy, such as going out more often, or playing golf, etc. Ironically, what is currently known, is that individuals would rather become couch potatoes than use oxygen.

Evidence supporting the use of AO, or advocating against its use, among exertionally hypoxic individuals with IPF could alter disease management by facilitating the development of treatment plans based on what is known about IPF, and not what is known about the obstructive lung diseases. The added knowledge could further help patients by adding to the body of data supporting, and increasing the awareness of, the benefits of AO. The HBM framework proposes that individuals with IPF are more likely

to use AO if they perceive the benefits associated with AO use as greater than its associated barriers. If AO can be shown to be of benefit, then the focus of care could shift to interventions such as CBT to empower individuals to break down the barriers that limit them from using AO, to enable them to use it in a way that may actually increase their HRQOL.

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