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Symptom Burden and Healthcare Utilization in Pulmonary Arterial Hypertension

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SYMPTOM BURDEN AND HEALTHCARE UTILIZATION IN PULMONARY ARTERIAL HYPERTENSION

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Abstract

Background: Pulmonary arterial hypertension (PAH) is a rapidly progressive disease. There is currently no cure; thus treatment is aimed at prolonging survival, improving functional status (FS), and symptom mitigation. Symptom burden (SB) can impact quality of life (QOL), and lead to increased healthcare utilization. Palliative care (PC) has been associated with higher QOL, decreased depression, aggressive care, and mortality. The Institute of Medicine's (IOM) recent report supports earlier integration of PC for people living with serious illness. Detection of patients at high risk for heavy SB may help to identify patients who could benefit from earlier integration of PC into standard care.

Objectives: Describe symptom occurrence and characteristics, and examine relationships between selected demographics, clinical characteristics, healthcare utilization patterns, and SB in patients with PAH.

Methods: A descriptive correlational study was conducted with a consecutive sample of PAH patients recruited at an academic medical center. Participants completed questionnaires at the time of their usual clinic visit. Demographics and perceived SB using the Memorial Symptom Assessment Scale (MSAS) were collected. A chart audit to collect clinical characteristics, and healthcare utilization patterns was completed. Data were analyzed with descriptive and correlational statistics.

Results: One hundred percent reported some symptomology. The mean number of symptoms reported was 16.0 (SD +/- 6.8), range of 1 to 29; three most common were, lack of energy (92%), shortness of breath (80%), and feeling drowsy (78%). Working patients, reported significantly lower Global Distress Index scores (GDI) (p = .006), physical

subscale scores (PHYS) ($p = .003$), and psychological subscale scores (PSYCH) ($p = .035$) compared to those not working. Patients who made more than 2 clinic visits within the previous six months had significantly higher GDI scores ($p = .001$), PHYS subscale scores ($p < .001$), and PSYCH subscale scores ($p = .035$). Patients receiving endothelin antagonists reported a statistically lower number of symptoms experienced ($p = .012$) compared to patient not receiving these medications. Patients on intravenous prostanoid therapy had more emergency department visits ($p < .001$) and hospitalizations ($p = .049$) compared to patients not on intravenous prostanoid medications.

Implications: Patients with PAH experience heavy SB. Patients with heavier reported SB include: those not working, not receiving endothelin antagonist medications, in FC III or IV, and those with more than 2 clinic visits in a 6-month period.

Dedication

This work is dedicated to my husband and son. Michael and Ariyan, you have supported me and sacrificed on behalf of my education many times over the last several years and I thank you from the bottom of my heart.

This is also dedicated to my deceased mother Catherine, whose incredible strength in life taught me much and helped guide my life's path.

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Chapter I
Introduction

Statement of the Problem

Symptom burden (SB) is the global appraisal of the symptom experience, which can result from both the disease process and its treatment. It is a healthcare priority due to its impact on the individual, the family unit, and society as a whole. The National Institute of Nursing Research (NINR, 2011) put forth their research priorities in 2011, which included symptom management and palliative care with goals of improving life quality in chronic and life threatening illness. "Specific research topics and activities include: relief of pain, suffering, and distressing symptoms through effective palliative care: understanding and facilitating decision making by patients, caregivers, and providers" (p. 19).

SB is a phenomena often associated with chronic and terminal disease, particularly cancer. In developing the measure, Symptom Experience Index (SEI), Fu, McDaniel, and Rhodes (2007) defined SB as the extent of physiological and psychological suffering resulting from a person's response to symptom manifestation. Cleeland (2007) spoke to the implicit negative connotations of symptoms in general, terming SB as a collective imposition of distress on a person. The self-regulation theory (Leventhal & Johnson, 1983) differentiates the experience of symptoms into the incidence of a symptom and the emotional distress associated with it. The latter aspect

could be considered SB. Suffering arising from symptom experience is influenced by the degree of perceived departure from one's baseline function, sensation, appearance, and the individual analysis of the value of these events (Rhodes et al., 2000). Thus symptom distress is the appraisal of the suffering and degree of burden.

Pulmonary arterial hypertension (PAH) patients are a unique population who face a heavy symptom burden associated with a myriad of factors related to the disease and its treatment (Ferrari et al., 2013; Khan 2011; Matura et al., 2012; Matura et al., 2014; Oudiz, 2012). Distinguishing aspects particular to PAH patients are the significant onus imposed by the inconvenience and side effects of the medication regimen, the lack of wider understanding regarding the disease which often heightens social isolation, and financial concerns of medications (Ferrari et al., 2013; Galie et al., 2009; Khan, 2011; Matura et al., 2010; Matura et al., 2014a; Matura et al., 2014b; McDonough et al., 2011; Oudiz, 2012). An adequate measure of SB is important in order to optimally measure improvements from medication adjustments or other interventions aimed at symptom mitigation such as palliative care integration. To date, there have been limited studies measuring SB in advanced PAH or patients in NYHA functional class III or IV. This proposed study's aims are to describe: demographics, clinical characteristics, and healthcare utilization patterns related to the SB experience of patients with advanced PAH.

Background and Significance

PAH is a rapidly progressive and chronic disease in which excessive proliferation of the smooth muscle and vasculopathy lead to constrictive remodeling of the pulmonary

vasculature (Galie, 2009; Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology ESC, 2009; Traiger, 2007). PAH has a myriad of etiologies with the majority arising from familial disease, idiopathic, or associated with other diseases. These conditions, in order of prevalence, include: collagen vascular disease, connective tissue disease which constitutes almost 50% of this subset, congenital heart disease (20%), portal hypertension (10%), drugs or toxins, (10%), HIV (4%), and other disease states (6%) (Badesch et al., 2010).

Pulmonary hypertension (PH) classification underwent revision at the 5th World Symposium on PH in 2013. The disease was broken down into two broad categories: PAH and non-PAH PH. Pulmonary arterial hypertension classification includes idiopathic: hereditary, drug or toxin induced, associated with, and a subclass of PAH. The "associated with" group has subgroups of connective tissue disease, HIV, portal hypertension , systemic-pulmonary shunts, schistosomiasis, and chronic hemolytic anemia (Table 1).

Table 1

Clinical Classification of Pulmonary Hypertension (PH)

1. Pulmonary Arterial Hypertension
    - Idiopathic
    - Hereditary
    - Drug/toxin induced
    - Associated with:
        - Connective tissue disease
        - HIV infection
        - Portal hypertension
        - Congenital heart disease
        - Systemic-pulmonary shunts
        - Schistosomiasis
        - Chronic hemolytic anemia

    1b. Subclass of PAH
        - Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
        - Persistent PH of the newborn
2. PH due to left heart disease
3. PH due to lung diseases and/or hypoxia
4. PH due to chronic thromboembolic pulmonary hypertension
5. PH due to unclear or multifactorial etiologies

Note. Adapted from Ferrari, P., Armstrong, I., Aldrighetti, R., Howard, L., Ryftenius, H., Fisher, A., ... Guillevan, L. (2013). *Impact of pulmonary arterial hypertension on the lives of patients and carers.* Presented at the 5th World Symposium on Pulmonary Hypertension, Nice, France.

The most definite diagnosis of PAH is achieved with a right heart catheterization to assess pulmonary artery pressures (PAP) (Lourenco et al., 2012). An elevated mean PAP of 25 mmHg or greater at rest or 30 mmHg or greater with exercise, a pulmonary capillary wedge pressure </=15, and a pulmonary vascular resistance of >/= to 240 dynes-sec-cm-5 (Badesch, et al., 2010; Lourenco, et al., 2012; Vachiery & Gaine, 2012) meet the criteria for diagnosis of PAH.

The pathology of PAH involves proliferation of the vessel's 3 layers: intimal, medial, and adventitial and encompasses at least three neurohormonal pathways: endothelin, nitric oxide, and prostacyclin. There is an imbalance of vasodilatation and vasoconstriction. As such, therapies have been developed that aim at addressing each pathway (Humbert et al., 2012b). Symptoms such as dyspnea, fatigue, angina, and syncope often present when the right ventricle (RV) is no longer able to effectively pump blood against the elevated pulmonary vascular resistance (PVR) (McGoon, et al., 2004). If left untreated the elevated PVR can lead to RV failure as measured by ejection fracture (EF) and cardiac index (CI) and ultimately early death (Champion et al., 2009). Without effective treatment the median survival of PAH is 2.8 years (Thenappan et al., 2010). There is currently no cure; thus treatment is aimed at prolonging survival and symptom mitigation.

The initial vague symptomatology may be attributed to deconditioning, stress, or anxiety, particularly in women, thus delaying appropriate diagnosis for years (Humbert et al., 2012a, Traiger, 2007). There is a higher prevalence among women (Pugh & Humes, 2010) with some estimates up to 3 times greater than males (Pugh & Hemnes, 2010).

With the creation of large registries such as the Registry to EValuate Early And Long-term PAH Disease Management (REVEAL) the preponderance of females afflicted with PAH has become indisputable (Badesche et al., 2010), yet the etiology remains elusive and seemingly multifactorial (Badesche et al., 2010; Pugh & Hemnes, 2010). The mean age of diagnosis of 50 (+/- 14) years is an age when women are often tasked with being caregivers, either for children, grandchildren, and/or parents. Nevertheless, there is a lack of research focusing on the female PAH population, or their perceived SB.

Advanced PAH patients may experience stress related to the uncertainty of their illness trajectory, the rapidness of the disease progression, the heavy symptom burden, and the complexity of their critical medication regimen. These factors can combine to place a patient at higher risk of depression (Matura & Carroll, 2010) and have a heighten effect on patients' psychosocial well-being (Khan, 2011). SB is a healthcare priority due to its impact on the individual, the family unit, and society as a whole.

Statement of Purpose

The purpose of this exploratory study is to describe the perceived SB experience of advanced PAH patients, and to examine relationships among select demographics (age, gender, race, education, marital status, living arrangements, and work status), clinical characteristics (time since diagnosis, medications, time on continuous intravenous therapy, right atrial pressure, cardiac index, pulmonary vascular resistance, NYHA functional class, and 6 minute walk test), and SB as measured by the Memorial Symptom Assessment Scale (Portenoy et al., 1994).

Aims

1. Describe the occurrence and characteristics (frequency, severity and distress) of perceived symptoms using the Memorial Symptom Assessment Scale (MSAS) among patients with pulmonary artery hypertension.
2. Examine the relationship between demographics (age, gender, race, education, marital status, living arrangements, and work status), clinical characteristics (time since pulmonary arterial hypertension diagnosis, medications, time on continuous IV prostacyclin if receiving it, New York Heart Association (NYHA) functional class, right atrial filling pressure (RAP), cardiac index (CI), pulmonary vascular resistance (PVR), and 6 minute walk test), healthcare utilization (number of clinic visits, emergency department visits and hospital length of stay within the previous 6 months), and symptom burden using the Memorial Symptom Assessment Scale (MSAS) among patients with pulmonary arterial hypertension.

Conceptual Framework

Three domains guide my personal conceptual framework. The first is topical research, which includes the review and critique of the literature and a review of gaps in regards to symptom burden in a pulmonary arterial hypertensive population. The second domain is my theoretical framework of which I have chosen the Revised Symptom Measurement Model and the Theory of Unpleasant Symptoms. The third domain regards my personal interest including personal beliefs and experiences. My beliefs system is affected by my theoretical and political leanings while my experiences include professional and personal understandings. As a critical care nurse for 15 years most of which was at a

facility world renowned for the treatment of pulmonary hypertension I have come to understand what it means to live and die with pulmonary hypertension in general. Being with patients and family members as they traversed the difficult world of critical care I saw how difficult decisions are in our present healthcare system with its priorities of technological advancement and postponement of death. The experience of being a recipient of healthcare for my mother with end stage lung cancer changed my practice dramatically. I became more empowered to take on an active role in the experience of patients and families facing difficult healthcare decisions as well as those at the end-of-life. Over time I have seen the benefits of incorporating palliative care into standard care for patients and families facing advanced illness.

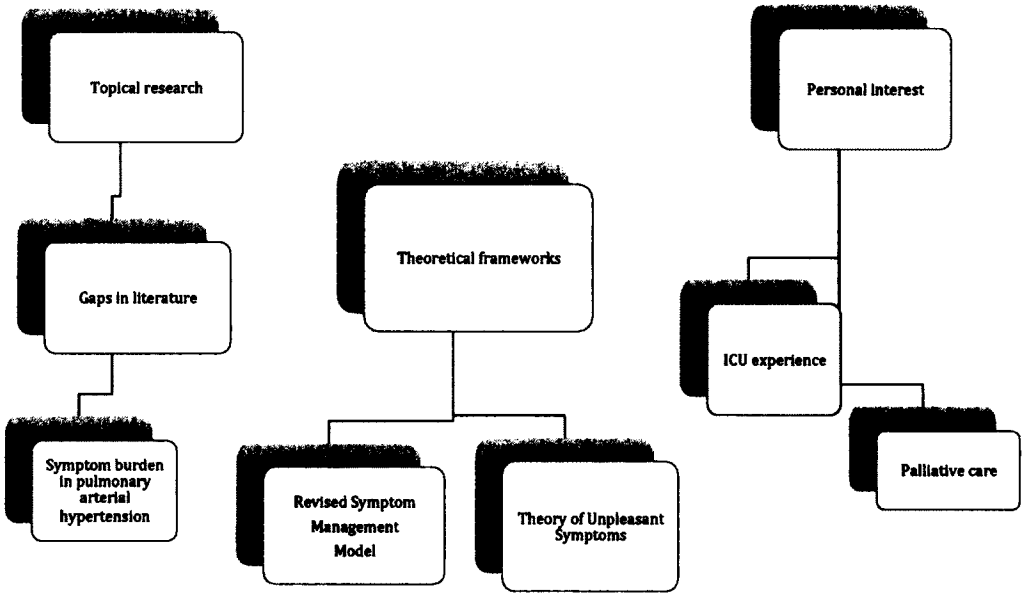

Figure 1. Madani conceptual framework.

Implication for Nursing

Assessing the PAH population at a medical center nationally recognized for the treatment of respiratory diseases will help to elucidate symptom burden perceptions, possible relationships with demographics, and clinical characteristics. Being able to optimally measure treatment efficacy for patients beyond the scope of the disease is necessary to understanding the full impact of an illness, as well as its accompanying treatment, and is at the center of patient-centered care.

The findings of heavy symptom burden in this population will help to underscore the need to integrate palliative care into standard care for all advanced PAH patients. Palliative care goals include assessment and treatment of physical and emotional distress, communication and decision making with patients and families to achieve patient centered goals, and coordination of transition care (Hospitals in Pursuit of Excellence, 2012). With early intervention by a multidisciplinary palliative care team, advanced PAH patients may experience less symptom burden, leading to increased functional status and QOL.

Clinical nurses are educated and prepared to care for a myriad of different disease states and levels of care. Healthcare has grown tremendously in technological advances over the last several decades, yet no concurrent education regarding communication and end of life care has occurred. Our medical therapies are sometimes extending the dying process rather than extending quality life. Properly prepared nurses are in a vital position to help clarify patients' goals of treatment. Our educational system needs to understand instruction regarding communication related to difficult decisions universal to nursing. Not all nurses will go in to specialties such as pediatrics or cardiovascular health, but all

will face the challenge of helping families navigate our healthcare system and be there for many difficult decisions. Palliative care is a subspecialty in the field of medicine, but for nursing it is at the center of our profession.

Chapter II

Background and Review of the Literature

The purpose of this research is to better understand the symptom burden (SB) experience in pulmonary arterial hypertension (PAH). This chapter and literature review will provide a critique and synthesis of the current body of knowledge regarding SB in PAH. It will provide a comprehensive overview of the state-of-the–science research on symptom burden in pulmonary arterial hypertension. An explanation of the method used to conduct the literature will be presented in the first section. The second section will examine the historical context of the symptom experience in PAH, gaps in the science related to symptom experience in PAH, and the need for further study in this area. In the third section the theoretical framework, UCSF Symptom Management Conceptual Model (SMCS) is portrayed to illustrate the concepts and their relationships between each other and within the model under study in this research. Next my personal conceptual framework is presented with this study placed within it, followed by theoretical definitions and measurements with analysis and synthesis of the literature specific to the variables in this study. The purposed instrument to measure SB will be presented and compared with alternative instruments. In the final section an analysis and synthesis of the literature specific will be conducted along

with an attempt to describe and understand symptom burden with particular consideration in an advanced PAH population.

Method of Literature Review

In conducting a thorough review of the literature relating to the symptom experience in PAH the following steps were followed: an electronic search was conducted among the following databases; PubMed, CINAHL, Google Scholar, Web of Science, ERIC, EMBASE, PsychINFO, and dissertation databases for articles with the following key words used for the article search strategy: symptom, symptom burden, symptom experience, symptom cluster, symptom distress, pulmonary hypertension, pulmonary arterial hypertension, and quality of life.

The list generated was then limited to English language articles relevant to pulmonary arterial hypertension, symptoms, and quality of life. After the initial electronic database search, a hand-search was also conducted on citations in the literature found to be relevant. Abstracts from meetings were included. The literature review contained, qualitative, descriptive, exploratory, interventional, and evaluation studies, as well as meeting abstracts, presentations, dissertations, and theses.

The literature synthesis highlights the many issues faced by patients with pulmonary arterial hypertension. Future research is needed to develop an interdisciplinary approach to mitigate symptom burden and improve quality of life for patients with PAH.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a progressive and chronic disease in which excessive proliferation of the smooth muscle and vasculopathy lead to constrictive

remodeling of the pulmonary vasculature (Lourenco et al., 2012; Traiger, 2007). There is currently no cure; thus treatment is aimed at prolonging survival and symptom mitigation.

Pulmonary hypertension (PH) is a general term for a myriad of causative factors and manifestations of elevated pulmonary pressures but has recently been categorized according to its etiology (Souza & Simonneau, 2014) (Figure 1). Group 1 is defined as pulmonary arterial hypertension. Group 1b is caused by pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. Group 2 is caused by left-sided heart disease. Group 3 includes causes related to lung disease or hypoxia. Group 4 is related to chronic thromboembolic causes, and group 5 includes unclear or multifactorial etiologies. Hemodynamic diagnostic criteria for pulmonary hypertension is an elevated mean pulmonary arterial pressure (PCWP) of > 25 mmHg. Pulmonary arterial hypertension is further differentiated with a normal pulmonary capillary wedge pressure of < 15 (Lourenco et al., 2012; Vachiery & Gaine 2012). The normal pulmonary capillary wedge pressure differentiates the pulmonary hypertension as pre-capillary PH or originating in the pulmonary vasculature as opposed to PH with PCWP of >15, which may signal post-capillary or pulmonary venous hypertension resulting from left heart disease. This differentiation is based on the assumption that PCWP is a surrogate marker for left ventricular end diastolic pressure.

Diagnosis. The differential diagnosis of PAH is difficult and not straightforward due to the insidious onset and non-specific early symptoms. The initial vague symptomatology may be attributed to deconditioning, stress or anxiety, particularly in women, thus delaying appropriate diagnosis for years (Traiger, 2007). An important step in the differential diagnosis process is elimination of other possible causes. Though some

progress has been made in non invasive technology to diagnosis, a right heart catheterization remains the gold standard for diagnosis (Vachiery & Gaine, 2012), while echocardiography remains a useful screening tool. Right heart catheterization can establish disease severity, test for vasoreactivity, and monitor for treatment effects. Due to the vague and subtle symptom display many patients are misdiagnosed for years. Symptoms such as dyspnea, fatigue, angina, and syncope often present when the right ventricle (RV) is no longer able to effectively pump blood against the elevated pulmonary vascular resistance (PVR) (McGoon et al., 2004). If left untreated, the elevated PVR can lead to RV failure as measured by ejection fracture (EF), cardiac index (CI), and ultimately early death (Champion et al., 2009). Early symptoms include: fatigue and dyspnea on exertion. Later symptoms are indicative of right heart failure and include: edema, ascities, chest pain, palpitations, and syncope (Humbert, Sitbon, & Chaouat, 2006). Pericardial effusions are an ominous indication of poor prognosis. Even with the diagnostic and treatment advancements made over the last several decades large registries are showing proper diagnosis remains prolonged with minimal to no improvement in the time to diagnosis. It has remained around 2-3 years (Badesch et al., 2010, Provencher et al., 2005) for the last few decades. Up to 70-80% of patients are in WHO functional class III or IV upon diagnosis (Frost, Badesch, & Barst, 2011; Vachiery, & Gain 2012). Without effective treatment the median survival of PAH is 2.8 years (Thenappan et al., 2010). There is currently no cure; thus treatment is aimed at prolonging survival and symptom mitigation.

Incidence and Prevalence. A clear picture of pulmonary hypertensions prevalence and incidence has not been formed due to the rarity of the disease and the

variety of etiologies. The incidence has been projected to be 2.4-7.6 cases/million/year and prevalence of 15-26 cases/million based on large population studies (Humbert et al., 2006, Peacock et al., 2007). Under diagnosis is an accepted reality for this population (Provencher et al., 2005). Prognosis is also difficult to calculate for the reasons listed above as well as for changing treatments, though newer registries demonstrate improvement in the last few decades. Three year survival improved from 48% (McLaughlin et al., 2004) up to 58-72% (McLaughlin & Suissa, 2010). Even with these improvements in PAH management, progression of the disease is inescapable for a majority of patients, thus long-term survival remains poor. There is a higher prevalence among women (Pugh & Humes, 2012) with some estimates up to 3 times that of males (Gaines & Rubin, 1998; Pugh & Hemnes, 2010). With the creation of large registries such as REVEAL the preponderance of females afflicted with PAH has become indisputable (Badesche et al., 2010) yet the etiology remains elusive and seemingly multifactorial (Badesche et al., 2010; Pugh & Hemnes, 2010). The mean age of diagnosis is 50 (+/- 14) years. This is an age when women are often caregivers, for their children, grandchildren, and/or parents. Many are still active in the workforce. Nevertheless, there is a lack of research focusing on the female PAH population or potential symptom management strategies most effective for women with PAH.

Pathophysiology. Pulmonary arterial hypertension can be hemodynamically defined as a mean pulmonary arterial pressure (mPAP) greater than or equal to 25 mm Hg with a concurrent pulmonary capillary wedge pressure (PCWP) of less than or equal to 15 mm Hg (Badesch et al., 2007) as measured by cardiac catheterization. It can be clinically defined as a collection of diseases characterized by a continual increase in

pulmonary vascular resistance leading to right ventricular resistance and premature death (Subias et al., 2010). There are a myriad of causes with the pathophysiology being multifactorial and opaque. Both genetic and environmental factors have been found to play a role in the mechanics and function of the pulmonary vasculature. It may occur in isolation of other disease states, or in conjunction, or as a result of other conditions. Regardless of the etiology the disease is a serious and progressive illness that leads to right ventricular failure and eventual death due to the inability of the right heart to generate enough pressure to pump blood forward into the pulmonary artery. Prognosis is related to these multifaceted interactions and their impact on the progression of the obstructive changes in pulmonary microcirculation, as well as the response of the right ventricle (RV) in working against these increased pressures. Elevated right heart afterload remains the main cause of heart failure in these patients.

This increased right heart afterload, as measured by PVR, results from pathophysiological changes in small arteries and pulmonary arterioles. A myriad of cellular and molecular factors lead to remodeling of the vessel walls via 4 basic mechanisms: vasoconstriction, cell proliferation, thrombosis, and immune factors (Subias et al., 2010). Despite a specific known origin, a genetic predisposition has also been suggested (Chan and Loscalzo, 2008). The resulting imbalance between vasodilatation and vasoconstriction with cell proliferation is the product of three main neurohormonal mechanisms. Medical therapy targets these three main neurohormonal pathways: nitric oxide, endothelin, and prostacyclin (Traiger, 2007, Lourenco et al., 2012), which will be described in greater detail under the management subheading.

Medical Management. New targeted therapies over the past 2 decades have improved overall survival with PAH, yet the impact of treatment can be incomplete and associated with persistent and heavy symptom burden (Swetz et al., 2012). Some patients can progress to the point of being ineligible or suboptimal for lung transplantation – thereby limiting treatment to the most aggressive medical therapeutics such as continuous intravenous medications. These medications possess a short half life- some as little as 2-5 minutes and must be infused 24/7 via a central line. Abrupt discontinuation could lead to rapid demise within minutes to hours. As such patients may feel tethered to their medication and burdened with the critical technical expertise required for the medication management. Another contributor to the stress of this disease may be the expense of the drugs, which can cost upwards of ten thousand dollars a month (Baesch, Abman, Simonneau, Rubin & McLaughlin, 2007). Vasodilation of the pulmonary vasculature leads to a reduction in right ventricular afterload, reduced workload of the heart, increased blood flow, and decreased pulmonary arterial pressure. All these factors lead to improvement in symptoms and exercise tolerance (Vane & Corin, 2003); the ultimate goals of medical treatment. Medical therapy targets the three main neurohormonal pathways: nitric oxide, endothelin, and prostacyclin. (Traiger, 2007; Lourenco et al., 2012).

Nitric Oxide Pathway. Nitric oxide (NO) is a powerful vasodilator produced in the lung vasculature endothelium by NO synthase (Humbert et al., 2004). It relaxes vascular smooth muscle by increasing the production of cyclic guanosine monophosphate. In PAH there is decreased endothelial NO synthase expression. Phosphodiesterase type-5 (PDE-5) is the chief enzyme responsible for the degradation of cyclic guanosine

monophosphate and is abundant in the lung. Inhalation of NO or inhibition of PDE-5, causes pulmonary vasodilatation (Traiger 2007). Phosphodiesterase inhibitors such as Sildenafil and Tadalafil are approved by the federal Drug Agency for treatment of PAH (Lourenco et al., 2012, Kingman & Lombardi 2013).

Endothelin Pathway. Endothelin is a protein with potent vasoconstrictor effects that induces cell proliferation in vascular smooth muscle and promotes fibrosis and inflammation. Endothelin acts on 2 receptors ETA, which are located on pulmonary vascular smooth muscle cells and ETB, which are located on pulmonary vascular endothelial cells and smooth muscle cells. ETA and their activation cause potent vasoconstriction by increasing the concentration of intracellular calcium. ETB receptors when activated cause vasodilatation via increased production of prostacyclin and NO in normal pulmonary vasculature. They also work in the clearance of endothelin. Treatment for PAH is aimed at blockage of both ETA and ETB receptors or selective blockage of ETA receptors (Traiger, 2007). Endothelin receptor antagonists have been shown to be effective in PAH patients with functional class II and III (Lourenco et al., 2012; Kingman & Lombardi, 2013).

Prostacyclin Pathway. The vascular endothelium produces prostacyclin from arachidonic acid. Prostacyclin possesses vasodilator, antiproliferative, and antiplatelet properties. Patients with PAH have been found with low levels of prostacyclin and decreased expression of prostacyclin synthase. Administration of prostanoid analogs produces comparable effects as endogenous prostacyclin (Kingman & Lombardi, 2013). Prostanoids are potent vasodilators that hold anti-thrombotic and anti-proliferative properties. They cause vasodilatation in the pulmonary vasculature and inhibition of

platelet aggregation via increasing cyclic adenosine monophosphate concentrations (Hackman & Lackner, 2006; Olschewski, Rose, & Schermuly, 2004). Due to the complexity of administration and follow up, patients receiving intravenous prostanoid formulations are usually cared for at experienced centers. Infusion requires a central line placement with the patient responsible for drug preparation and infusion, as well as central line management (Lourenco et al., 2012). Side effects include; headache, flushing and sudden death following abrupt discontinuation (McLaughlin et al., 2009).

Oral treatments such as phosphodiesterase type -5 inhibitors (Sastry, Narasimhan, Reddy, & Raju, 2004, Zhao, Mason, & Morrell, 2001) and endothelin receptor antagonists (Channick, Simonneau, & Sitbon, 2001, Rubin, Badesch, & Barst, 2002) have been effective in patients with mild to moderate PAH. For patients with advanced PAH unresponsive to conventional therapies intravenous prostacyclin therapy continues to be one of the most effective treatments (Barst, Rubin, & Long, 1996; Rubin, Mendoza, & Hood, 1990).

Combination therapy. Research to support combination therapy is new but growing (Lourenco et al., 2012) as it offers healthcare providers a way to target more than one neurohormonal pathway in order to improve clinical efficacy and decrease side effects.

Symptom Experience in PAH

New targeted therapies over the past 2 decades have improved overall survival with PAH, yet the impact of treatment can be incomplete and associated with persistent and heavy symptom burden (Swetz et al., 2012). Some of these medications possess a short half-life: as little as 2-5 minutes and must be infused 24/7 via a central line. Abrupt discontinuation could lead to rapid demise within minutes to hours. Inhaled modalities

may need to be administered up to 25 times a day. As such, patients may feel tethered to their medication and burdened with the critical technical expertise required for the medication management.

PAH is a serious disease with unique issues that may have a heighten effect on patients' psychosocial well-being (Khan, 2011) and place a patient at higher risk of depression (Matura & Carroll, 2010). Pulmonary arterial hypertension patients on IV medications may experience stress related to the uncertainty of their illness trajectory, the rapidness of the disease progression, the heavy symptom burden and the complexity of their critical medication regimen. SB is a high healthcare priority due to its impact on the individual, the family unit, and society as a whole.

Theoretical Framework

Revised Symptom Management Model (RSMM)

The Revised Symptom Management Model (Dodd, Janson, Facione, & Froelicher, 2001) is an evidence-based nursing model which underwent revision based on years of research conducted at UCSF nursing school from the original proposed model put forth by Lenz, Pugh, Milligan, Gift, and Suppe (1997). This is a comprehensive model describing the symptom experience and influencing factors. Within the global overlapping and interconnected nursing domains of person, environment, and health/illness lies the triad of dimensions of the symptom management model: symptom experience, symptom management, and outcomes, which also possess interwoven relationships and influences.

Assumptions integral to this model include: (1) the self-reporting of the individual experiencing the symptom is considered the gold standard, (2) the experience of a symptom is not a requisite to apply this model. Simply being at risk in enough to warrant intervention

strategies, (3) interpretations of the symptom experience by caregivers of patients unable to verbalize their symptom experience such a infants are assumed to be correct for assessing and intervening, (4) the focus of interventions may be the individual, a family, group, or work environment level, and (5) the process of symptom management is a dynamic, and influenced by the nursing domains of person, environment, and health/illness.

This research will be examining the RSMM concepts of symptom experience and symptom status. Specifically, morbidity to assess a relationship between symptom burden, morbidity, disease progression, and patient demographics as they exist within the nursing domains of person and disease/illness.

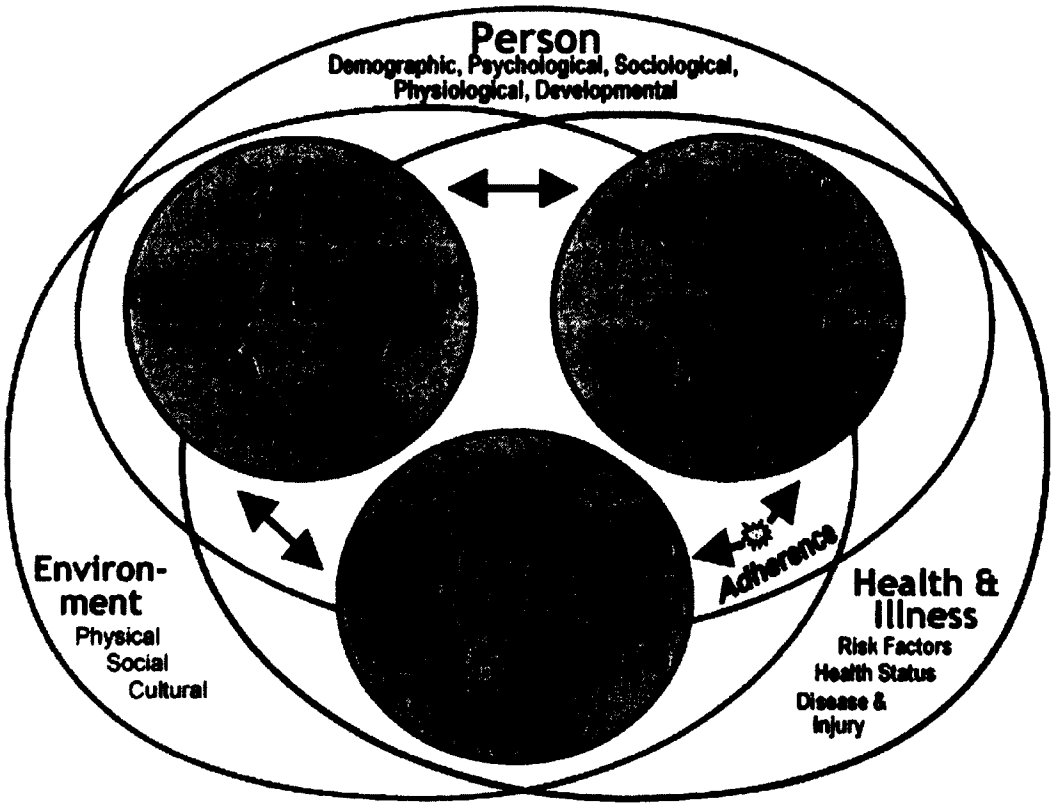

Figure 2. Revised Symptom Management conceptual model. Adapted from Dodd, Janson, Facione, & Froelicher, 2001.

The Middle Range Theory of Unpleasant Symptoms

The Theory of Unpleasant Symptoms was first introduced in 1995 and was further developed and updated in 1997 (Lenz et al., 1997; Lenz & Pugh, 2003). The theory possesses three major components of the symptom experience. The first contains influencing factors of situational, psychological, and physiological aspects that impact the symptom experience. Psychological components such as anxiety and depression have been shown to impact the experience of a variety of symptoms (Blinderman, Homan, Billings, Portenoy, & Tennstedt, 2008, Blinderman, Homel, Billings, Tennstedt, & Portenoy, 2009, Dodd et al., 2001, Ferrari et al., 2013). Situational factors include the social environment and perceived social support. Variability in patients' symptom experience can be attributed to psychological factors such as anxiety and depression and to situational factors such as social support.

The second component is the symptom experience itself, which contains dimensions of distress, timing, intensity, and quality of the symptom experience. These dimensions are assumed to be discreet yet related. The time dimension consists of frequency, duration, and timing related to certain activities. It is considered the extent to which the individual is bothered by it. The distress dimension most closely correlated with symptom burden and most contributes to quality of life. According to this theory it is how individuals understand the experience and whether symptom mitigation is pursued.

The third component is performance, which speak to consequences of the symptom experience on three levels: functional status, cognitive functioning, and physical performance. This holistic theory speaks about the common occurrence of

multiple symptoms manifesting simultaneously and the synergistic effect that may occur. The experience of symptom is multifaceted, fluid, and dynamic.

This theory has many parallels to the RSMM but RSMM also possesses the domain of symptom management. This is important for a mid range theory to possesses as it is less abstract and more purposeful and directional than a grand theory. This helps to increase the applicability of the theory in clinical practice, as well as measure outcomes. Early work with this theory was done with the symptoms of dyspnea and fatigue; two prevalent symptoms in advanced pulmonary arterial hypertension.

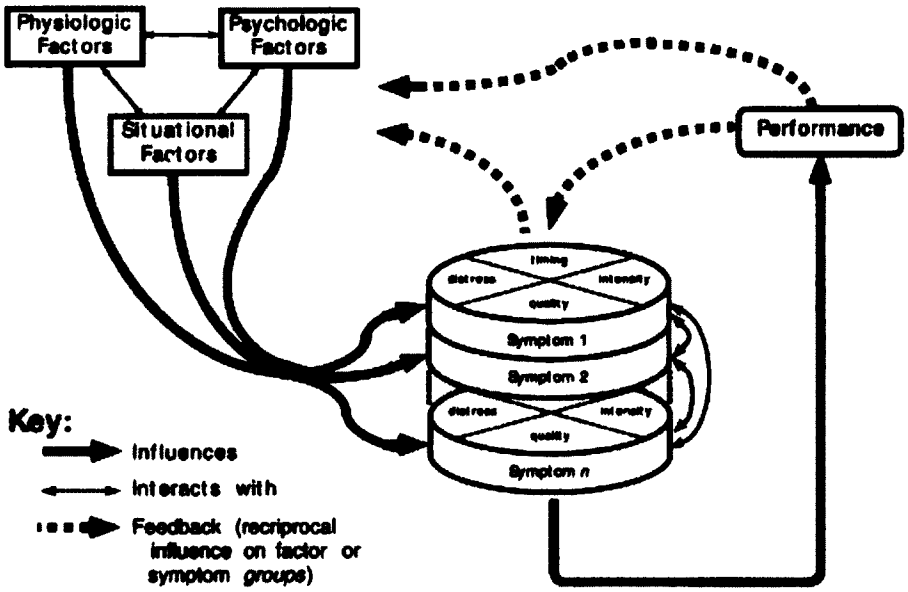

Figure 3. Theory of Unpleasant Symptoms conceptual model. Adapted with permission from Lenz, E. R., & Pugh, L. C. (2003). *The theory of unpleasant symptoms*. In M. J. Smith & P. R. Lehir, P. R. (Eds.), Middle range theory for nursing. New York, NY: Springer.

Conceptual Framework

The conceptual framework for this study is heavily influenced by the philosophy of palliative care. According to the National Consensus for Quality Palliative Care's 2009 clinical guidelines for quality palliative care (National Consensus Project for Quality Palliative Care 2009):

> The goal of palliative care is to prevent and relieve suffering and to support the best possible quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies. Palliative care is both a philosophy of care and an organized, highly structured system for delivering care. Palliative care expands traditional disease-model medical treatments to include the goals of enhancing quality of life for patient and family, optimizing function, helping with decision-making, and providing opportunities for personal growth. As such, it can be delivered concurrently with life-prolonging care or as the main focus of care.

Patients with advanced PAH are excellent candidates for the integration of palliative care into their standard treatment as they face unique multidimensional issues. In addition to many functional and life limiting symptoms, PAH patients face unique challenges a few of which include: critical medication management, social isolation, and financial concerns regarding the cost of medications. A better understanding and measure of SB in this population could help to evaluate the impact of palliative care services, as well as help to predict patients that could benefit most from this integration of care.

One fifth of all health care spending in the US is consumed by the costliest 1% of the population. This group receives most of their care in a hospital setting with insufficient healthcare coordination (Agency for HealthCare Research and Quality, 2009). Advanced pulmonary arterial hypertension patients exemplify these concerns. Due to the

cost of their medication regiment they are often refused by hospices and rehabilitation centers, leaving them in hospital setting unnecessarily for prolonged periods of time. Palliative care may help to mitigate improper care by assisting with healthcare decisions and symptom management, as well as providing patient-centered care.

Symptom Burden

Symptom. The word symptom originates from the Greek word symptoma meaning "anything that has befallen one" (Cleeland, 2007, p. 17). Merriam-Webster (2012) defines symptom as, "subjective evidence of disease or physical disturbance." Gapstur (2007) grouped meaning according to the specialty of the literature and from the medical literature she derived the definition: "Symptoms are known to be the subjective evidence of illness or disease that signify a change in normal cellular function" (p. 674). The concept analysis of symptom management by Fu et al. (2004) found the literature to conclude a symptom was subjective and experiential, with major dimensions of symptoms being occurrence, distress, and experience. Within the dimension of symptom occurrence are frequency and duration.

Burden. Merriam-Webster (2012) reports burden as, "something that is carried: Load, duty, responsibility, something oppressive or worrisome." Synonyms listed are: load, encumber, freight, lade, laden, lumber, saddle, and weight. In the psychology literature Possemato (2010) referred to disease burden in Veterans as, the aggregate of medically diagnosed conditions. The mother of the writer of this paper used the phrase "cross to bear" that conjures up a rather frightful image to convey her idea of a heavy

burden or onerous lot in life. In looking at the concept it is important to note burden consistently possesses implicit negative connotations in the literature (Cleeland, 2007).

The theory of unpleasant symptoms (Lenz et al., 1997) describes distress, as the extent to which a person is disturbed by a symptom and suggests its perception is influential in whether a person seeks to continue aggressive treatment or palliation. Distress is also the element with the greatest impact on quality of life. Distress, worry, and oppression are analogous in the symptom experience.

Symptom Burden. Symptom Burden is a phenomena often associated with chronic and terminal disease, particularly cancer (Gaspur, 2007). Other disease progressions that have attempted to understand SB include, hemodialysis (Weisbord et al., 2003); COPD (Klinkenberge, Willems, van der Wal, & Deeg, 2004), heart disease (Ruo et al., 2004), chronic critical illness (Nelson et al., 2004), inflammatory bowel disease (Farrell & Savage, 2010), and diabetes (Ludman et al., 2004). Though there is recent work looking at symptoms of PAH (Ferrari et al., 2013), there is a dearth of information looking specifically at the burden of living with this advanced disease and its treatment.

Gapstur (2007) conducted a concept analysis of symptom burden with an oncologic focus, in which she found a consistent report of the adverse effects of symptoms on quality of life (QOL), physical, social, and psychological functioning, as well as cost of treatments and hospitalizations. The definition produced from her concept analysis is "the subjective, quantifiable prevalence, frequency, and severity of symptoms that place a physiologic burden on patients and may produce multiple negative physical, psychological, and emotional patient responses" (p. 667). Fu, McDaniel, and Rhodes (2007) in the development of the Symptom Experience Index (SEI), defined SB as the

extent of physiological and psychological suffering resulting from a person's response to symptom manifestation. Gough, Smith, Ross, Riley, and Judson (2011) reported SB in a sarcoma population as the experience of symptoms resulting from the disease or its accompanying treatments. Cleeland (2007) spoke to the implicit negative connotations of symptoms in general, terming SB as a collective imposition of distress on a person.

The self-regulation theory (Leventhal & Johnson, 1983) differentiates the experience of symptoms into the incidence of a symptom and the emotional distress associated with it. The latter aspect could be considered SB. The suffering arising from symptom experience is influenced by the degree of perceived departure from one's baseline function, sensation, appearance, and the individual analysis of the value of these events (Rhodes et al., 2000). Thus symptom distress is the appraisal of the distress and degree of burden.

Gapstur (2007) differentiates symptom burden from distress, but by only a miniscule margin. Untangling the nuances may not be time well spent. The literature conflates symptom distress and burden in many disease states (Cleeland, 2007; Farrell & Savage, 2010; Fu et al., 2004; 2007). Burden by its definition implies distress, thus suffering is implicit in the symptom burden experience. Instruments measuring SB measure distress and or severity, such as the Condensed Memorial Symptom Assessment Scale (Weigand & Kalowes, 2007), Symptom Experience Index (Fu et al., 2007), Adapted Symptom Distress scale (Rhodes et al., 2000), and Memorial Symptom Assessment Scale (Joyce, Akbar, & Khan, 2008, Portenoy et al., 1994). The literature supports the terms symptom distress, burden, and severity as equally measuring the negative impact of symptom

experience. Now the focus should be on instruments to optimally measure and mitigate negative consequences of symptom experience.

Critical Attributes of Symptom Burden

Subjective Perception/Appraisal of Distress. Symptom burden is the individual appraisal and response to the experience of a symptom and possible distress. Core aspects of the appraisal include, perception, evaluation of the meaning of the experience, and response (Farrell & Savage, 2010; Fu et al., 2004; 2007). Cleeland (2007) described SB as the patient's summative perception of the impact and severity of symptoms from tumor or treatment burden, and contrasted the individual's subjective observance and report of a symptom, against "signs" of disease, which are empirically measureable. Symptoms are a subjective experience that may be amplified by the perception of the symptom(s) infringement upon the patient's lifestyle and relationships, as well as their perceived ideal vision of themselves or role attainment before illness (Lazarus & Folkman, 1984). One of the constructs in the cognitive adaption model is appraisal, which can be described as how a person understands an experience. It suggests people go thru a primary and a secondary cognitive appraisal in response to a stressor. Initially a person will assess the relevance and threat of a situation. The second step is more complex but can be summarized as an evaluation of one's coping strategy options (Lazarus & Folkman, 1984). A patient's perception of their SB is determined by their appraisal of impact on their lives and quality of reserves to cope (Newness, 2011). This aspect of stress appraisal is integral to the symptom burden experience.

Dynamic. Symptom burden is a fluid phenomena that ebbs and flows according to the multidimensional factors' interactions and their relationship of continuous reciprocity

(Dodd et al., 2001). Examples include: the context of the symptom, the patients' disease progression, treatment (if any), as well as the physiological, psychological, and social response to both. (Dodd et al., 2001; Fu et al., 2004; 2007; Gapstur, 2007). According to the theory of unpleasant symptoms the expression of symptoms may differ in regards to the intensity, quantity of associated distress, timing, and quality (Farrell & Savage, 2010).

Multidimensional. Symptom burden has a myriad of contributing, initiating, and exacerbating factors. Subsets of multidimensional include: physiological, psychological, and social (Dodd et al., 2001; Gapstur, 2007). Physiological dimensions can be further broken down into frequency, prevalence, and intensity (Farrell & Savage, 2010; Gapstur, 2007; Lenz & Pugh, 2003). Social dimension can be affected by a person's age, gender, culture, values, education, health knowledge, disease, treatments, beliefs, and past experiences (Fu et al., 2004). There was divergence in the literature with some authors looking at the three dimensions and others only counting the number of symptoms as a representation of multidimensionality (Gapstur, 2007). For SB to be considered multidimensional it must possess more than a single dimension of the symptom experience.

The Theory of Unpleasant Symptoms (Lenz et al., 1997) is comprised of three major concepts: the experience of the symptom, influencing factors, and consequences of the experience. Every symptom is a multidimensional occurrence that may ensue in isolation or in combination with other symptoms from a disease or its treatment. Aspects of the symptom experience are timing, intensity, quality, and distress. Influencing factors on the symptom experience are categorized as physiological, psychological, and situational which is akin to social factors.

The largest study to date looking at the impact of PAH on patients' lives found three overall dimensions of symptom impact: physical, social, and psychological. As the patients functional status increased so did the burden of their symptoms (Ferrari et al., 2013). Two distinguishing aspects particular to PAH patients is the significant burden imposed by the inconvenience and side effects of the medication regimen (McKenna et al., 2006), and the social isolation associated with an orphan disease and a misinformed public (Ferrari et al., 2013; Wryobeck, Lippo, McLaughlin, Riba, & Rubenfire, 2007).

Empirical Referents for Symptom Burden

Empirical referents measuring critical attributes of SB can be differentiated according to the attribute. For perception of distress the referents include: evaluation, degree, or impact of distress of the symptom experience. For the attribute dynamic the referents are: frequency, intensity, quality, and timing. The attribute multidimensional has referents of physical, psychological and social impact on daily living such a functional ability and status.

When SB is not adequately managed patients tend to come into the emergency room for assistance in managing their symptoms and may be admitted to the hospital. Thus ED visits and hospital admissions with diagnosis, length of stay, pain scale, and prescribed medication regimen would be empirical referents.

Theoretical Definitions and Measurements

Demographics. Demographic data will be collected by a self-report and will include: gender, age, ethnicity, marital status, education, and employment (Appendix B).

These are important concepts as purported by the RMCM model and fall under the dimension of person, and environment.

Gender. The initial vague symptomatology may be attributed to deconditioning, stress or anxiety, particularly in women, thus delaying appropriate diagnosis for years (Traiger, 2007). There is a higher prevalence among women, with some estimates up to 3 times greater odds (Pugh & Hemnes, 2010). With the creation of large registries such as REVEAL the preponderance of females afflicted with PAH has become indisputable (Badesch et al., 2010), yet the etiology remains elusive and seemingly multifactorial. Nevertheless, there is a lack of research focusing on the female PAH population or potential symptom management strategies most effective for women with PAH.

Age. The mean age of diagnosis in PAH is 50 (+/- 14) years (Badesch et al., 2010). This is an age when people are often caregivers, for their children, grandchildren, and/or parents. Many are still active in the workforce.

Ethnicity, marital status, education, and employment have been measured in previous studies in the PAH population along with quality of life (Badesch et al., 2010, Batal et al., 2011, Ferrari et al., 2013, Hwang, Howie-Esquivel, Fleischmann, Stotts, & Dracup, 2012; Matura & Carroll, 2010, Matura et al., 2012b) and symptom burden studies with other medical diagnoses (Blinderman et al., 2008; 2009, Cleeland, 2007; Fu et al., 2004).

Clinical Characteristics. Clinical characteristics fall within the domain of Health and Illness in the RMSM model and impact the symptom experience.

NYHA Functional Class. The New York Heart Association's nomenclature for functional classification was first proposed in 1928 and has since been revised several

times with the most recent revision in 1994. The status has been shown to be associated with disease progression (Humbert, Sitbon, & Simonneau et al., 2004, New York Heart Association, 1964), serves as a measure of disease severity as a measure of exercise intolerance, and is used as an approximate measure of the provider's opinion of the patients' functional status in clinical trials.

Class I refers to patients with cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or angina pain. Class II refers to patients who have cardiac disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina pain. Class III patients have cardiac disease that results in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitations, dyspnea or angina pain.

Class IV patients with cardiac disease results in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased (New York Heart Association, 1964).

Six minute walk test. The six-minute walk test is a noninvasive and simple test measuring the distance a person is able to walk within 6 minutes. It has been found to correlate well with functional exercise capacity, disease progression, mortality, and is an established outcome in clinical trials (Humbert, Sitbon, & Simonneau et al., 2004). The general cut off for a healthy walking distance is considered to be greater than 333 meters (Humbert et al., 2012a).

Right atrial pressure. The right atrial pressure, also known as central venous pressure is a measure of the blood in the thoracic vena cava near the right atrium of the heart. It is a surrogate for preload or the amount of blood returning to the heart and the ability of the heart to pump the blood forward. It can be measured via echocardiography, heart catheterization, or with a central line and bedside monitoring. (Subias, Mir, & Suberviola, 2010). The tip of the catheter is attached to a transducer, which reads the pressure being exerted by the blood inside the right atrium. The transducer produces a waveform that consists of a, *c,* and *v* waveforms. The *a* wave represents atrium contraction, the *c* wave represents tricuspid valve closure, and the *v* wave represents ventricular contraction which causes the valve to bulge into the atrium.

Right atrial pressure is regulated by a balance between the ability of the heart to move blood out of the right heart and through the left heart into the systemic circulation, as well as the amount of blood returning to the heart from the systemic circulation. The normal range of CVP is 0-5 mmHg. Possible causes of an elevated CVP include an inability to fill adequately due to such causes as congestive heart failure, hypervolemia, cardiac tamponade, or vasoconstriction, which affects the ability of the heart to empty its chambers. Decreased pressure may be indicative of hypervolemia (Urden, Lough, & Stacy, 2010). Right atrial pressure is a vital indictor of right heart function and disease progression in PAH (Humbert et al., 2004).

Cardiac index. Cardiac output represents the amount of blood volume pumped out by a ventricle. Cardiac output is a function of heart rate per minute multiplied by the volume of blood pumped by the heart with each contraction, i.e. stoke volume (ml/beat), e.g. CO = HR x SV. In comparison, cardiac index is the volume of blood pumped by the

heart per minute divided by the individual's body surface area. It is considered to be a more accurate measurement since it is based on an individual's height and weight. Normal CI range is 2.2-4.0 L/min/ m2 (Urden et al., 2010), and is used as an indicator of overall cardiac function, as well as disease progression in PAH (Humbert et al., 2004).

Pulmonary vascular resistance. PVR is a measure of the right heart's afterload or mean pressure difference across the pulmonary vascular bed, divided by blood flow. Clinically, this value represents resistance that the right ventricule must overcome in the pulmonary arteries and arterioles in order to eject the blood volume and move the blood volume forward. As the pressure in the pulmonary vasculature increases the output from the right ventricle decreases. It is usually measured in dynes/sec/cm-5, with normal pressures ranging from 100 – 250 dynes/sec/cm-5 (Urden et al., 2010). In the left side of the heart the left ventricle must pump against the pressure in the systemic circulation or aorta and is referred to as system vascular resistance or SVR. Increased afterload remains a main measurement of heart failure in PAH (Humbert et al., 2004; Subias et al., 2010,).

Months Since Diagnosis and Months on IV or SQ therapy. The length of time a patient has been living with PAH and receiving more advanced medical therapy may be relevant to their symptom burden.

Symptom Burden

The instrument to measure psychological and physical symptom burden for the study was the Memorial Symptom Assessment Scale (MSAS) (Portenoy et al., 1994). The MSAS is a patient self-reported instrument to assess the occurrence, characteristics, and extent of symptom burden. Twenty-six physical symptoms and six psychological symptoms

are measured on 4 or 5-point Likert scales assessing how often, severe, and how much distress is associated with each symptom. This measure includes: the overall number of symptoms experienced, the average total score of each symptom across the three dimensions of frequency, severity and associated distress (MSAS- Total), and three main symptom burden subscales: physical symptom distress subscale (PHYS), psychological symptom distress subscale (PSYCH), and the global distress scale (GDI). The mean score of six psychological symptoms is the PSYCH subscale score: worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, and difficulty concentrating. The PHYS subscale is the mean of the 26 physical symptoms. The GDI subscale is purported to be a gross measure of the perceived global symptom distress and is considered the most clinically useful measure of the MSAS (Portenoy et al., 1994). It is comprised of the frequency scores the following four psychological symptoms: worrying, feeling sad, feeling nervous, and feeling irritable, and the distress scores from the following six physical symptoms: pain, lack of energy, lack of appetite, constipation, feeling drowsy and dry mouth. The MSAS and it subscales have been used to study the effects of symptoms as a predictor of survival (Chang, 2004), while the total number of symptoms experienced on the MSAS has correlated with a spiritualty measurement tool (Peterman, 2001).

In the MSAS's initial psychometric analysis two major factors related to meaningful grouping of symptoms emerged. One group, named PSYCH, contains 6 symptoms relating to psychological status. It can be divided into a subgroup with 4 symptoms that are emotional in type named EMOT, and a subgroup termed CONC with 2 symptoms: difficulty sleeping and concentrating. In this study the six symptoms of the

PSYCH subscale were used without teasing out the smaller EMOT and CONC subgroups due to their small number. Another larger group, named PHYS H, has 12 frequent physical symptoms. The third and final group is named PHYS L, which contains 15 physical symptoms that occur with less frequency compared to PHYS H. In this study the PHYS subscale used to capture all 26 physical symptoms. The 12 frequent physical symptoms comprising the PHYS H subscale are considered the MSAS-PHYS subscale (table 6). The MSAS-Total subscale is the average of the dimensions scores for each symptom. This score is not considered to be a strong clinical indicator of symptom burden (Chang, et al., 2004; Portenoy, et al., 1994).

The initial population the MSAS was normed with was an oncology population. It has since been psychometrically tested in varying chronic illness and cultures (Chang et al., 2004; Weisbord et al., 2003). The MSAS-SF has been utilized most widely in patients with cancer and AIDS, where it has been shown to have good reliability and validity (Portenoy et al., 1994) (Weisbord et al., 2003). The Cronbach alpha coefficients for internal reliability were 0.882 for the PHYS H. The coefficient for PSYCH grouping was 0.835. The coefficients for group PHYS L was lower at 0.580. Reliability will be computed with the study sample prior to data analysis. Recently, the MSAS has been shown to be a valid and reliable measure of symptom burden in two similar population; congestive heart failure and chronic obstructive pulmonary disease (Blinderman et al., 2008; 2009).

Table 2

Components of Memorial Symptom Assessment Scale (MSAS) Subscales: Psychological (PSYCH) Symptoms, Physical (PHYS) Symptoms, and Global Distress Index (GDI)

Subscale	Symptom
MSAS PSYCH	
	Difficulty concentrating
	Feeling sad
	Feeling nervous
	Difficulty sleeping
	Feeling irritable
	Worrying
MSAS PHYS	
	Pain
	Lack of energy
	Nausea
	Feeling drowsy
	Feeling bloated
	Vomiting
	Lack of appetite
	Dizziness
	Changes in the way food tastes
	Weight loss
	Constipation
MSAS GDI	
Average frequency score of the following psychological symptoms	
	Feeling nervous
	Feeling sad
	Worrying
	Feeling irritable
Average distress score of the following physical symptoms	
	Pain
	Lack of energy
	Lack of appetite
	Feeling drowsy
	Constipation

Note. Portenoy, R. K., Thaler, H. T., Kornblith, A. B., Lepore J. M., Friedlander-Klar, H., Kiyasu,... Norton, L. (1994). The Memorial Symptom Assessment Scale: An instrument for the evaluation of symptom prevalence, characteristics and distress. *European Journal of Cancer, 30A*(9), 1326–1336.

Healthcare Utilization Measurements

The sickest 10% of the US population accounts for more than half of its healthcare expenditures (Zuvekas, 2007 #132). One fifth of all health care spending in the US is consumed by the costliest 1% of the population. This group receives most of their care in a hospital setting with insufficient healthcare coordination (Agency for HealthCare Research and Quality, 2009). Advanced pulmonary arterial hypertension patients exemplify these concerns. Due to the cost of their medication regiment they are often refused by hospices and rehabilitation centers, leaving them in hospital setting for prolonged periods of time unnecessarily. Insufficient outpatient support and coordination of care can lead to misuse of acute care services. Interdisciplinary services such as palliative care may help to mitigate improper care by assisting with transitions of care, symptom management, and healthcare decisions by establishing patient and family-centered goals and working to help the patient achieve those goals. Quality palliative care (PC) can benefit the patient and their family foremost, but may also help to achieve the Institute of Healthcare Improvement's (IHI) tripe aim of: improving patients' experiences of care (including quality and satisfaction), improving the health of populations, and reducing the per capita cost of healthcare (Berwick, Nolan, & Whittington, 2008).

Pulmonary Hypertension Clinic Visits. Patients living with PAH are usually seen by their PH specialist every three to six months depending on the stability of their disease progression and medical management. Non-pulmonary clinic visits were not recorded. This was determined by the name of the attending for the visit listed in the electronic medical record. Only pulmonary specialist visits were recorded. The number of

clinic visits in a six-month visit could be a red flag for providers to take a closer look at patient's symptom burden and possible need for initiating a palliative care consult.

Emergency Department Visit and Hospital LOS related to PAH. Both of these metrics were recorded as additional measures of healthcare utilization within the previous six-month time frame.

Literature Analysis and Synthesis

As noted previously studies have shown incongruence between HRQOL measures and symptomology. Though HRQOL measures have been shown to be prognostic for survival they also remain too generic for symptom response to medical management, thus a better understanding of the concept of SB may help to more accurately measure patient reported outcomes, and a more specific symptom assessment is needed to elucidate the symptom experience of patients and understand medication side effects, as well as treatment response.

HRQOL measures emphasize physiological aspects of QOL regarding treatment that may or may not improve functional performance, symptoms or physical dysfunction, however anxiety and depression are significant players in the QOL measurement. Despite the awareness that QOL is a subjective and dynamic concept the need for empirical measurement overrides this discussion of its merit to measure such things. Previous studies in PAH have pointed out the shortcomings of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) to adequately assess symptomology (Matura et al., 2014). The CAMPHOR is the initial measure for assessing patient-reported symptoms, functioning and QOL specifically for pulmonary hypertension (Gomberg-Maitland et al., 2008). This instrument was shown to be reliable and valid yet

the instrument itself does not allow for answers to be on a continuum and may miss out on more detailed information (Matura et al., 2014). Respondents mostly may choose only dichotomous answer choices; true/false or yes/no answers. There is also no measure of the associated distress from the symptoms, which is a vital aspect of the Revised Symptom Management Model (Dodd et al., 2001).

In a study looking at predictors of QOL in an idiopathic PAH population, patients with less functional ability, had decreased physical health status, HRQOL, and increased psychological distress. HRQOL predictors included symptom and activity totals on the US CAMPHOR, role emotional on the SF-36, depression scores on the POMS, employment status, and oxygen use (Matura et al., 2012b). This study underscores the need for nursing to focus on symptoms and response to treatment in caring for PAH patients.

Two reviews of the literature of the human response to and psychological aspects of PAH described the need for a better understanding of the prevalence and impact of symptoms, both psychological and physical, experienced by PAH patients in order to develop effective interventions to be developed and tested. (Matura & Carroll, 2010; Wryobeck et al., 2007).

Although there has been limited qualitative work done in this population, two qualitative studies specifically on the patient's experience of PAH were found. The samples were well matched with the large registries on PAH. Khan (2011) interviewed a majority of functional class three participants. Interviews were conducted via phone as a means to encourage responses "without much thought" thus providing a more neutral answer. Two overriding themes emerged from this work, "holding back" and "redefining life". The

predominant issues were fear of breathlessness and the uncertainty of the disease trajectory. Breathlessness was related to either "taking things slowly" or a "fear of blacking out". Medication issues tended to reside within both themes, with the aspects of activity limitation falling under holding back and practical medical necessities such as maintaining a central line and oxygen therapy related to the redefining life theme. Adjustment to medication regimen fell under redefining life along with the stoicism needed to "accepted their medical situation". Flattery, Pinson, Savage, and Salyer (2004) used a phenomenological approach to examine the lived experience of PAH with a sample of 11.Two overarching themes emerged: uncertainty of the disease progression and other aspects of the disease, as well as learning to cope with the illness.

The largest study to date looking at the global impact of PAH on patient and caregiver's lives was conducted in 5 European Union countries (Ferrari et al., 2013). The first phase of the study was qualitative and consisted of 40 patient and caregiver interviews; 25 patients and 15 caregivers. The second phase was a quantitative questionnaire distributed to 455 individuals; 326 patients with PAH and 129 care givers of patients with PAH. The aim of this large-scale study was to provide new understanding(s) of the global impact of PAH on patients and care givers beyond the clinical definition of the physical weight of the disease, which had not been comprehensively researched. The four main areas inspected included: the physical and practical impact of PAH, the emotional impact, the financial impact, and information needs and requirements to better understand PAH patients' and care givers' experience of living with PAH. As the patients functional status increased so did the encumbrance of their symptoms. Results underscore the need to offer comprehensive care that assesses

emotional and social well-being, as well as physical symptoms and understanding these needs increase as functional class increases. Educational provisions regarding PAH should include financial, social, and emotional aspects of the disease and its treatment. These findings point to the importance of incorporating palliative care into the standard care of PAH patients, especially as they progress to functional class III and IV. Three dynamic dimensions of symptom burden in PAH emerged from this study. The physical dimension consists of functional class. The social dimension speaks to the isolation of having an orphan disease whose physical presentation can often belie the true limitations of the disease. This often creates a lack of understanding and compassion from those close to the patient, as well as the community at large. The third dimension of symptom burden in PAH is psychological, which is impacted by emotional and financial situations, as well as social aspects of living with the illness. Both patients and caregivers felt healthcare professionals provided inadequate information to them, with patient organizations as the major source of information and support. The present gap in care delivery is highlighted by this study. Palliative care could assist families understand and work through difficult healthcare decisions to ensure they are in alignment with their family's goals of care.

Standard QOL measurements, as well as those particular to chronic lung or heart disease do not properly reveal the clinical status or prognosis of persons with PAH (Rubenfire et al., 2009). Other pulmonary disease metrics do not apply to PAH because it is a circulation problem not an alveolar problem. Presently there is no adequate measure of the symptom experience in PAH.

Summary

Literature on PAH speaks to the burden of living with the disease and its treatment (Ferrari, et al., 2013; Khan, 2011; Matura et al., 2014a; Oudiz, 2012). Distinguishing aspects particular to PAH patients are the significant onus imposed by the inconvenience and side effects of the medication regimen, the lack of wider understanding regarding the disease which often heightens social isolation, and financial concerns of the medication (Ferrari, et al., 2013; Khan, 2011; Matura et al., 2006; McDonough & Carroll, 2012; Oudiz, 2012).

Cleeland (2007) suggested symptom burden could have specific attributes specific to different disease trajectories. Patients with PAH face unique multidimensional issues, yet no measure has been developed to adequately measure PRO specific to this population. This study will be a step towards achieving this goal.

Symptom burden can be considered analogous to carrying a cross. It is the weight of the symptom experience. The appraisal of onus is subjective and experiential on the patient's part, yet a measure of distress is implicit in the symptom burden experience. Being able to optimally measure symptom treatment efficacy for patients beyond the scope of the disease is vital to understanding the full impact of an illness, as well as its accompanying treatment, and is at the center of patient-centered care.

CHAPTER III

Methodology

The purpose of this study was to examine the relationship between demographics, clinical characteristics, and symptom burden (SB) in a pulmonary arterial hypertensive (PAH) population. Additionally, it will describe a sample of people living with PAH who have not previously been studied regarding SB and healthcare utilization. This chapter offers a detailed description of the research design, sampling, instrumentation, and analytic techniques. The protection of human subjects is also discussed.

Aims

1. Describe the occurrence and characteristics (frequency, severity and distress) of perceived symptoms using the Memorial Symptom Assessment Scale (MSAS) among patients with pulmonary artery hypertension.
2. Examine the relationship between demographics (age, gender, race, education, marital status, living arrangements, and work status), clinical characteristics (time since PAH diagnosis, medications, time receiving IV prostacycline if receiving it, New York Heart Association (NYHA) function class, right atrial pressure (RAP), cardiac index (CI), pulmonary vascular resistance (PVR), and 6 minute walk test), healthcare utilization patterns (number of clinic visits,

emergency department visits and hospital length of stay within the previous 6 months), and symptom burden using the Memorial Symptom Assessment Scale (MSAS) among patients with pulmonary arterial hypertension.

Research Design

A descriptive cross-sectional, correlational design was used for this study. The purpose of a descriptive correlational design is to examine the direction and magnitude of relationships that may exist in particular situations (Polit, 2010). A descriptive correlational study is specified as a study conducted in a naturalistic setting without any attempt to manipulate, control, or introduce something new to the setting (Kerlinger & Lee, 2000). It is also useful to obtain information in areas in which minimal or no research has been previously done. This method is optimal for obtaining the specific aims identified by exploring the relationship between symptom burden, demographics, and clinical characteristics, as they presently exist.

Setting and Sample

A consecutive convenience (purposive) sample of adult ($\geq$18 years old) pulmonary arterial hypertension (PAH) patients were recruited from a tertiary, academic hospital system, which serves as a national referral center for pulmonary hypertension patients in the southwest United States over a 6-month period. Consecutive sampling plan was employed due to its superior approach in mitigating sample bias. By attempting to recruit all members of an accessible population, bias risk can be deeply reduced (Polit & Beck, 2012). Specialists at this tertiary academic institution were encouraged to offer participation to all qualifying patients. Eligible patients include patients diagnosed with

PAH, ≥18 years of age, and able to speak and read English. Exclusion criteria include, participants with a serious or unstable medical or psychological condition that in the opinion of the principal investigator would compromise participation in the study or had a coexisting illness unrelated to PAH that may confound the assessment and non-English speaking.

Anticipated refusal rate was 10%. This correlates with a typical expected drop out rate (Polit & Beck, 2012), and intrinsic motivation to participate in research that may benefit others living with the same disease. People with orphan disease may have stronger ties or a sense of responsibility to help improve the lives of others with their disease. Due to the smaller number of people afflicted with PAH they may possess a greater sense of collaboration or duty. The anticipated drop out rate is 10% due to SOB or loss of interest during the expected 10 minutes needed to complete the survey.

Power Analysis

The necessary sample size for this study was determined by calculating the effect size, the desired power, and an acceptable significance level. In order to determine significance of statistical results an adequate sample size must be utilized to minimize the possibility of making a type II error. With Pearson correlations the estimated value of estimate size is p, the population correlation coefficient (Polit & Beck, 2012). With an estimated population correlation of .30 (medium effect size), a power level of .80, and alpha of 0.5 a sample of 85 was needed to avoid a type II error.

Data Collection Procedures

Subject Recruitment and Enrollment

The PAH specialist RN was asked to identify eligible patients as they presented for routine office visits or if they were inpatient at the hospital over a seven month period; October 2013 through April 2014. Pulmonary arterial hypertension patients are seen by their pulmonologist every 3 to 6 months if they are stable on their present treatment, more often if they are not. The PAH specialist nurse recruited participants at the time of their routine scheduled clinic visit. She provided all potential participants with a recruitment flyer as part of clinic check in at the time of their scheduled clinic visit. She assessed for interest to participate after the patient had time to read the flyer in the waiting area or clinic room. Written informed consent from each participant was obtained after explaining and discussing the study by the PAH specialist nurse or primary investigator (Appendix A).

Data Collection Protocol

Interested participants were provided with an information letter on the study that included: (a) an overview of the study, (b) name and phone number of the principal investigator, (c) information regarding the right to refuse participation by not completing the questionnaires, (d) their ability to withdraw from the study at anytime, (e) a guarantee of confidentiality, (f) a UCSD IRB approved letter of consent (Appendix A), and a UCSD IRB approved Request for HIPPA waiver to access medical records. Those willing to participate were provided a packet containing a consent form to participate in the study and to access their medical record, an Experimental Subject's Bill of Rights, and a survey comprised of demographic, and healthcare utilization questions (Appendix B) and the MSAS (Appendix C) during their visit. The estimated time to complete the packet was 10 minutes. The packet

and signed consents were completed by the participants and collected during the same clinic visit by the PAH specialist nurse or PI. The primary investigator, through chart review, collected clinical characteristics data and healthcare utilization information such as the number of emergency department visits, hospitalizations and clinical visits related to their PAH diagnosis in the previous six months (Appendix D). Electronic data are stored on a password-protected computer and written information related to this study is being kept in a locked office at UCSD.

Variables/Instruments

Demographics

Data were collected on the following selected demographic items: age, gender, race, education, marital status, living arrangements, and work status (Appendix B).

Clinical Characteristics

Clinical data to be collected include, time since PAH diagnosis, PAH related medications, years on IV prostacycline if receiving it, New York Heart Association (NYHA) functional class, central venous pressure (CVP), cardiac index (CI), pulmonary vascular resistance (PVR), and 6 minute walk test (Appendix D).

Healthcare Utilization Pattern

Healthcare Utilization was measured by the number of emergency department visits, hospitalizations, and clinical visits the patient had in the previous 6 months related to their PAH treatment. Healthcare utilization related to other diagnosis was not recorded. These data were collected on both the patient and investigator measure to help identify patients who needed a more detailed chart review and to help mitigate missing data.

Memorial Symptom Assessment Scale (MSAS)

The instrument to measure psychological and physical symptom burden for the study was the Memorial Symptom Assessment Scale (Portenoy et al., 1994). The MSAS was developed to provide a multidimensional picture of prevalent symptoms in patients with diverse types of cancer. Since its inception it has been adapted and used in other chronic illness such as HIV, congestive heart failure, and chronic obstructive pulmonary disease (Blinderman et al., 2008; 2009, Selwyn et al., 1999) as well as clinical trials (Chang et al., 2004). It is a self-report measure, which includes 32 symptoms common to cancer and three dimensions relevant to symptom evaluation: the severity of the symptom experience, the frequency with which the symptom occurs and, the distress associated with the symptom. For six symptoms in which frequency was not relevant, only severity and distress are measured. Separate four or five-point Likert scales were created for the three dimensions for all the symptoms. The average of each symptom score across the three dimensions is referred to as the MSAS-Total score. The total overall number of symptoms reported by an individual is also considered to be clinically relevant. The three subscales capable of being be calculated are: physical symptom distress subscale (PHYS), psychological symptom distress subscale (PSYCH), and the global distress scale (GDI). The mean score of six psychological symptoms is the PHYS score. The mean score of 12 prevalent physical symptoms constitutes the PHYS subscale. The mean distress score of six physical symptoms and frequency scores four psychological symptoms form the GDI score. The range of subscale scores is 0 (minimal distress) to 4 (maximal distress). The MSAS has been utilized widely in patients with chronic illness, where it has been shown to have good psychometric properties of reliability and validity (Blinderman, et al., 2008; 2009; Chang, et

al., 2004; Portenoy, et al., 1994; Weisbord, et al.,2003). The Cronbach's alpha for the physical subscale is 0.88, and for the psychological subscale is 0.84. Reliability was tested with the study sample prior to data analysis. Cronbach's Alpha coefficients for PSYCH, PHYS, GDI subscales were .947, .920, and .821 respectively.

Data Analysis

Data were screened for distribution patterns and outliers. Missing data and outliers were individually checked in the electronic medical record and on data collection forms. Descriptive data were reviewed on all variables with scatterplot diagrams, mean, median, and mode for continuous variables and frequencies for ordinal or categorical data. Data were checked for meeting assumptions of normality, linearity, and homogeneity of variance before conducting a Person's correlation coefficient. Initial bivariate correlation was conducted on all key variables before conducting other analyses.

Data are described as mean +/- standard deviation for normally distributed variables, as median with minimal and maximal values for skewed variables, and as percentages for categorical variables. To explore factors associated with overall symptom burden, the global distress index (GDI) score was considered the primary outcome for all bivariate analyses. In bivariate analysis the GDI score was used for Pearson correlations with other variables. Categorical variables were dummy coded in order to calculate correlations. All tests used a significance level of $p=/< 0.05$. The data were analyzed using SPSS 21 (SPSS, Inc., Chicago, IL, USA). Data analysis of the instruments were utilized as follows:

Memorial Symptom Assessment Scale. Memorial Symptom Assessment Scale (Portenoy et al., 1994) was used to measure symptom burden (Appendix A). MSAS

subscale scores were included in the analyses. The MSAS subscale GDI, as the measurement for symptom burden, was the continuous dependent variable and the focus of this study.

Pearson's Product-Moment Correlation Coefficient

The most widely used correlation index is the Pearson's product-moment correlation coefficient (Pearson's r), which can be used with two variables on interval or ratio scale measurement. The correlation coefficient clearly communicates the size of a relationship but there are no specific rules for interpreting the strength of a correlation coefficient (Polit, 2010). An important aspect of this correlation coefficient is the ability of its square (r^2) to be a direct indication of the proportion of the variability in one variable that can be explained by variability in another variable.

Other Measures of Association

In addition to Pearson's r, there are other statistical measures that explain relationships between two variables and allow inferences about relationships in the population. For ordinal-level variables, or variables that have non-linear relationship Spearman rank order correlation coefficient were used (Polit, 2010). Dichotomous variables were analyzed using Point Biserial correlation or student t-tests.

Strengths and Limitations of Methods

This study is considered a feasibility study due to the limited sample size of 49, which was short of the sample size of 85 calculated by the power analysis. Even at a nationally recognized PAH center the sample size was not able to meet the power analysis requirements for size. Despite this limitation this study may be the largest study looking specifically at advanced PAH patients receiving continuous intravenous therapies.

Protection of Human Subjects

In order to ensure the protection of each subject's freedom from intrinsic risk or injury and to maintain rights to privacy, and dignity a variety of human subject protective mechanisms were utilized in this study. Coercion avoidance was achieved via verbal and written statements that participation is completely voluntary. Approval for the proposed study was obtained from the University of San Diego Investigational Review Board (Appendix E), and the University of California San Diego Investigational Review Board (Appendix F), along with an approved recruiting script (Appendix G). Patients were assigned a personal identifier, which was used for all data entry and analysis. Only aggregate data will be presented in publications or presentations. The findings will be used to enhance current knowledge in the care of pulmonary arterial hypertension patients.

Summary

This quantitative research study implemented a descriptive correlational design to identify the relationship between symptom burden, demographics, disease and treatment related variables, and healthcare utilization. An initial estimate of 60 adult advanced pulmonary arterial hypertension patients were anticipated to participate in this study. The participants answered a demographic, disease, treatment, and healthcare utilization questionnaire, as well as the Memorial Symptom Assessment Scale to measured symptom burden. The primary investigator performed chart extraction for specific clinical and healthcare utilization data. Data were analyzed using descriptive statistics, including Pearson's correlation coefficient and Spearman rank correlation coefficient.

CHAPTER IV

Results

The purpose of this exploratory study was to (1) describe the occurrence and characteristics (frequency, severity, and distress) of perceived symptoms using the Memorial Symptom Assessment Scale (MSAS) among patients with advanced pulmonary artery hypertension (PAH) and (2) to examine the relationship between demographics (age, gender, race, education, marital status, living arrangements, and work status), clinical characteristics [time since PAH diagnosis, medications, time receiving intravenous prostacycline if receiving it, New York Heart Association (NYHA) functional class, right atrial pressure (RAP), cardiac index (CI), pulmonary vascular resistance (PVR), and 6 minute walk test], healthcare utilization (clinic visits, emergency department visits, and hospitalization in the previous 6-months), and symptom burden using the Memorial Symptom Assessment Scale (MSAS) among patients with pulmonary arterial hypertension. In this chapter a discussion of the findings will be presented in three sections. The first section, will present a description of the sample. The second section will present a description of PAH symptom characteristics, and finally bivariate analyses are presented.

Characteristics of the Sample

A demographic questionnaire (Appendix C) was designed to collect demographic and personal data from participants to create a sample profile, along with a chart extraction form for electronic medical record data collection by the PI. Patient reported data included: age, gender, race, marital status, education, work status, living arrangements, PAH medications, use of intravenous PAH medication, if yes, then length of time receiving it. The chart extraction tool (Appendix D) collected the following data: number of clinic visits in the past 6 months, emergency room visits in the past 6 months, hospitalizations in the past 6 months, right atrial pressure (RAP), cardiac output (CO), cardiac index (CI), pulmonary vascular resistance (PVR), 6-min walk test, and New York Heart Association's (NYHA) functional class.

The sample included 49 PAH patients screened from PAH clinics of a large teaching hospital during October 2013–April 2014 (seven-months). Of the patients seen in clinic during this time 54 patients were enrolled and consented. Patients with PAH are usually seen by their pulmonary specialist every 3 or 6 months depending on the severity of their illness. The seven-month window of recruitment was to capture as many patients with advanced disease and/or on multiple medical therapies, as possible. Patients not recruited were seen in clinic when either the PI or a co-researcher was not involved in the clinic to recruit. Of the 53 consented participants four did completed less than 25% the questionnaires and were not included n the final analyses.

Patient Characteristics

Participant age ranged from 18 to 80 years, with a mean age of 49.5 (SD +/- 14), and a median age of 48.0, (Table 3). The sample was predominantly female (90%) and white (61%). Other racial compositions included 27% Hispanic/ Latino, 8% African American, 4% Asian. Marital status broken down in descending order: Married (37%), Divorced (29%), Separated (12%), Widowed (2%), and Never-been-married (20%). Most participants lived with family or friends (86%) versus living alone (14%). None were in facilities. The vast majority of participants had at least some college education (76%), 25% were college graduates, 51% had some college, 20% had some high school, and 4% had less than a high school diploma. Two thirds of the participants work status was classified as disabled (67%), while 14% were retired, 12% were working full-time, and 6% were working part-time.

Table 3

Demographics of Participants (N = 49)

Sex	*n*	%
Female	44	90
Male	5	10
Age, years Mean(SD)	49.5 (13.8)	
Race		
White	30	61
Hispanic	13	27
Other (Asian and African American)	6	12
Marital status		
Married	18	37
Divorced	14	29
Separated	6	12
Single—Never married	10	20
Widowed	1	2
Education		
Some high school	2	4
High school graduate	10	20
Some college	25	51
College graduate	12	25
Work status		
Full-time	6	12
Part-time	3	6
Retired	7	14
Disabled	33	68
Living arrangements		
Lives alone	7	14
Lives with friends/family	42	86

Clinical Characteristics

Pulmonary arterial hypertension clinical characteristics indicated the average length of time since diagnosis for participants was 6.8 years (SD = 5.0), with a range of less than a year to 20 years. Clinic visits averaged 2.6 (SD = 1.3) over the previous six-month period. A quarter of participants were admitted to the hospital with a mean length of stay (LOS) of 9.5 days (SD = 28.1), with a range of 2 to104 days.

Table 4

Clinical Characteristics of Participants (N = 49), Mean, and Range

linical Characteristic	**N (%)**	**Mean (+/- SD)**	**(Range)**
Time since diagnosis	49	6.8 (5.0)	(0,20)
Clinic visits	49	2.6 (1.3)	(0,5)
Emergency Department visits	49	0.5 (.8)	(0,3)
Hospital admissions	49	0.39 (0.7)	(0,3)
Length of stay (*n* = 12)	12 (24.5)	16.4 (28.1)	(2,104)
Right atrial pressure	48	10.4 (4.9)	(2,24)
Cardiac output	49	4.5 (1.4)	(2.1, 7.9)
Cardiac index	49	2.6 (0.7)	(1.2, 4.1)
Pulmonary vascular resistance	46	700 (348)	(80, 1721)
6-Minute walk test	44	396.2 (99.4)	(210, 602)
NYHA Functional Classification System	49	*n*	%
Class II	23(46.9)	23	46.9
Class III	22 (44.9)	22	44.9
Class IV	4 (8.2)	4	8.2

Note. NYHA, New York Heart Association.

Time Since PAH Diagnosis. Eighty-one percent of participants had their PAH diagnosis for at least 10 years, while 53% of participants had their PAH diagnosed 5 years or less. Time since diagnosis in years is not a normally distributed variable according to its skewness and kurtosis coefficients. Skewness coefficient was .902, which is more than twice its standard error (.340). Kurtosis was -.398, which is less than twice its standard error (.668). Thus, this variable did not meet the assumption of normality and non-parametric test were used with this variable. Median time since PAH diagnosis was 5 with a range of zero to twenty.

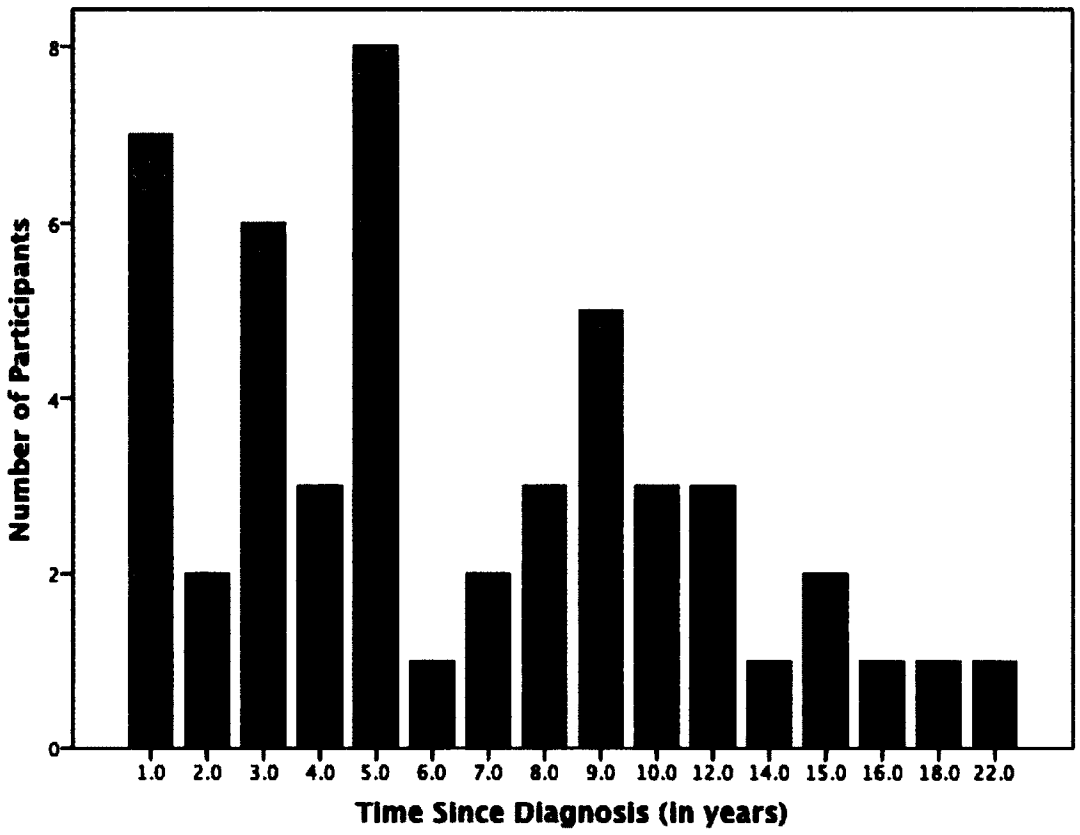

Figure 4. Time (years) since pulmonary artery hypertension diagnosis.

Time receiving intravenous prostanoid therapy in years. Forty three percent of participants were receiving intravenous of subcutaneous infusions of PAH medications. Of the participants receiving continuous infusion therapy, 15 (71%) had been on treatment for 3 years or less.

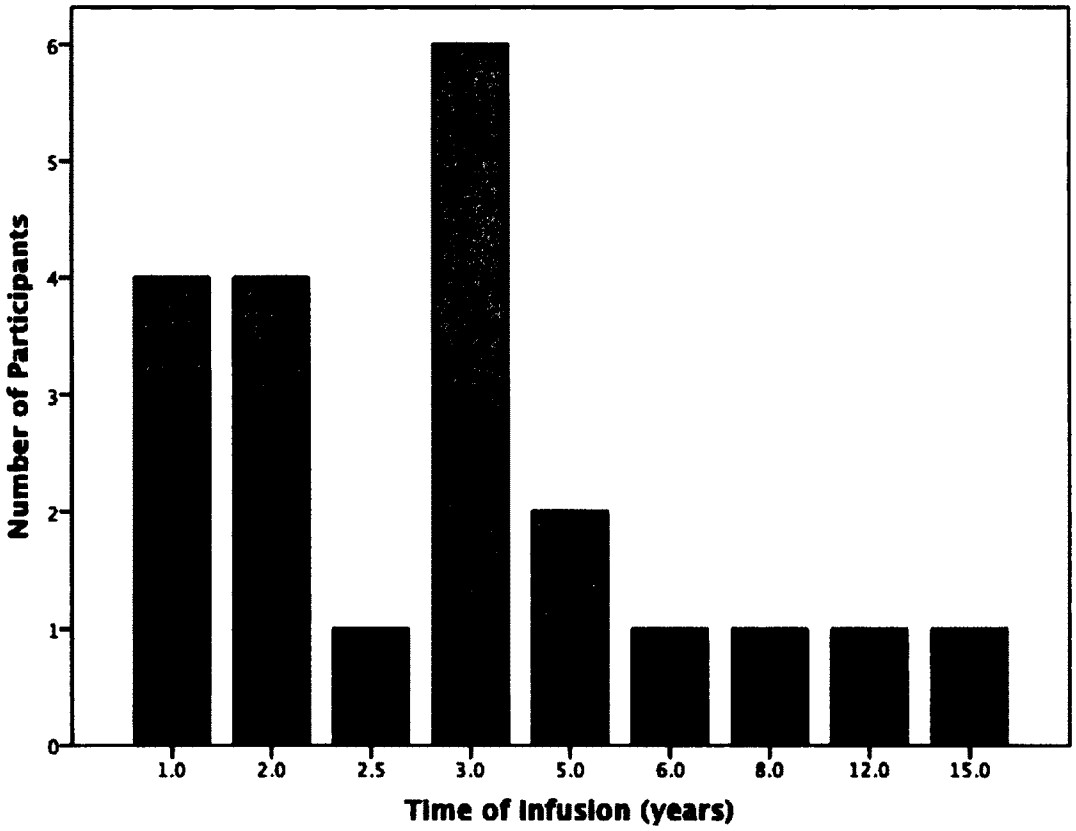

Figure 5. Time (years) of intravenous infusion.

Pulmonary Specialty Clinic Visits in the Previous Six-months. Forty three percent (n= 28) of patients had 3 or more PAH clinic visits in the previous six months.

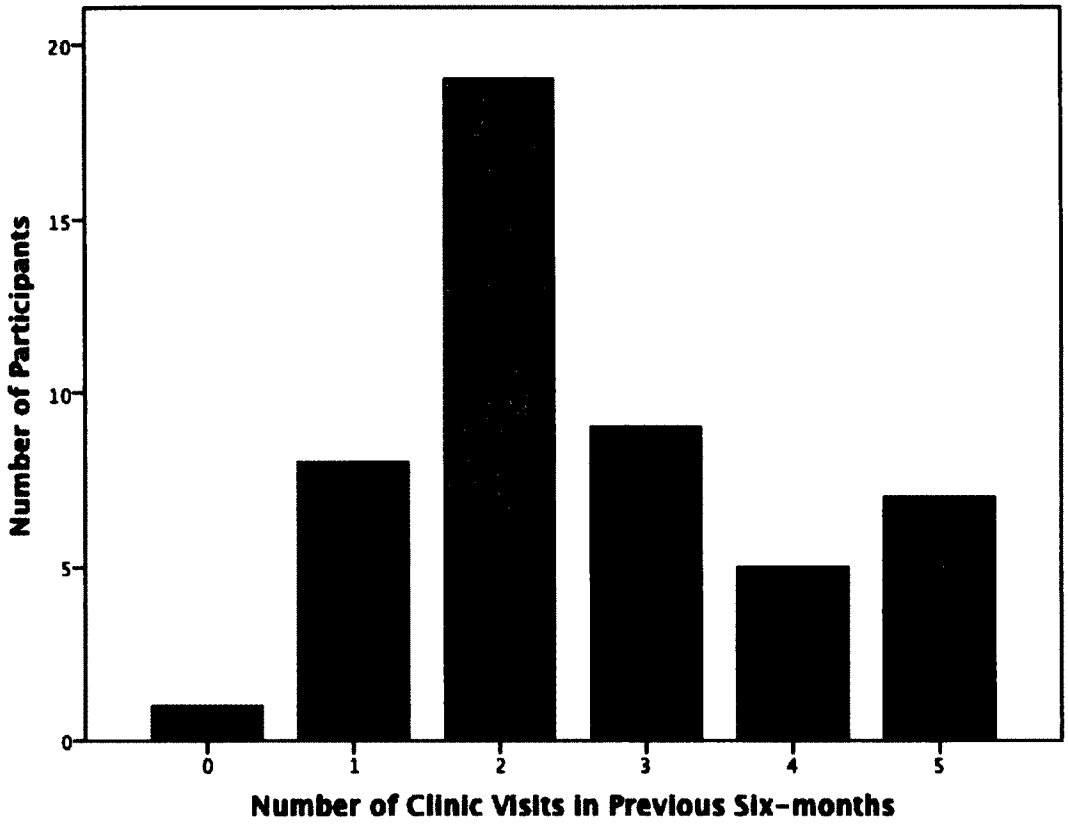

Figure 6. Number of clinic visits in the previous six-months.

Emergency Department visits in the previous six months. Fifteen (31%) participants had been to the emergency department in the previous six months for an issue related to their PAH. The most common causes included, infected access, occluded access, and fluid overload.

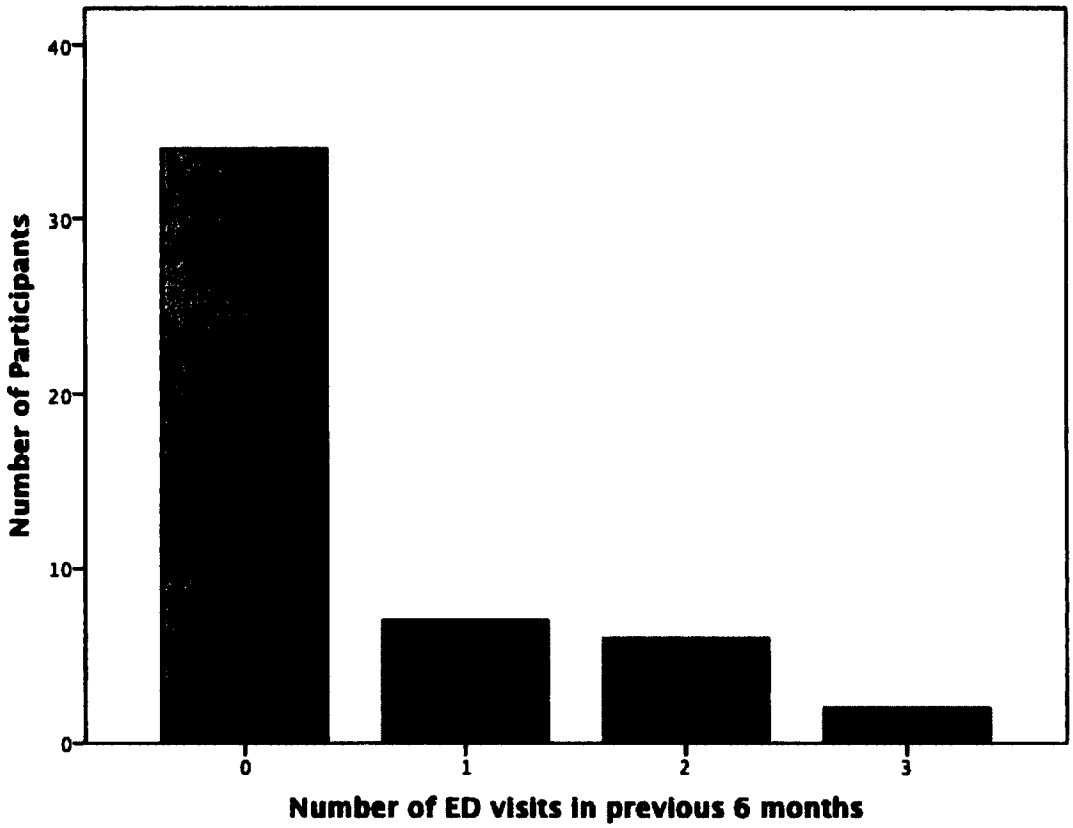

Figure 7. Number of Emergency Department (ED) visits in previous six-months.

Hospital Admissions and Length of Stay (LOS) in the previous six-months. Fourteen patients (29%) were admitted to the hospital for a clinical need related to their PAH diagnosis, with a total of 12 patients staying longer than 24 hours. The median LOS was 9.5 days with a range of 2 to104 days. Most patients who were admitted to the

hospital (92%) were there for less than 20 days. One outlier was in the hospital for 104 days due to difficulty finding placement in the community related to the management of their medical regimen. The total inpatient days for PAH patients were 197 days over 209 hospital days.

Right atrial pressure. The right atrial pressure, also known as central venous pressure is a measure of the blood in the thoracic vena cava near the right atrium of the heart. It is a surrogate for preload or the amount of blood returning to the heart and the ability of the heart to pump the blood forward. The normal range of CVP is 0-5 mmHg. Possible causes of an elevated CVP include an inability to fill adequately due to such causes as congestive heart failure, hypervolemia, cardiac tamponade, or vasoconstriction, which affects the ability of the heart to empty its chambers. Decreased pressure may be indicative of hypervolemia (Urden et al., 2010). Right atrial pressure is a vital indictor of right heart function and disease progression in PAH (Humbert et al., 2004). The mean RAP for this sample was 10.43 with a standard deviation of 4.9.

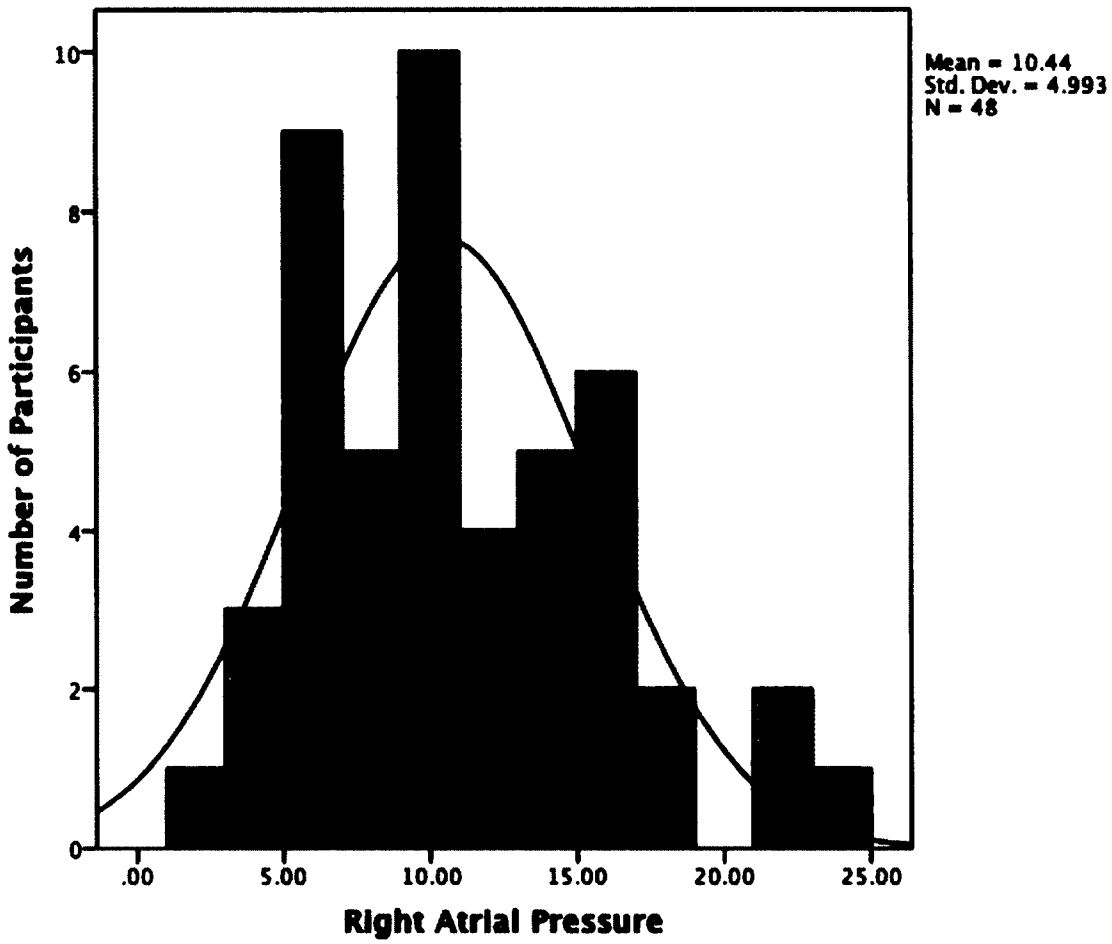

Figure 8. Right atrial pressure (RAP).

Cardiac index. Cardiac output represents the amount of blood volume pumped out of by a ventricle. Cardiac output is a function of heart rate per minute multiplied by the volume of blood pumped by the heart with each contraction, i.e. stoke volume (ml/beat), e.g. CO = HR x SV. In comparison, cardiac index is the volume of blood pumped by the heart per minute divided by the individual's body surface area. It is considered to be a more accurate measurement since it is based on an individual's height

and weight. Normal CI range is 2.2-4.0 L/min/ m2 (Urden et al., 2010), and is used as an indicator of overall cardiac function, as well as disease progression in PAH (Humbert et al., 2004). The mean CI for this sample was 2.55 with a SD of .71.

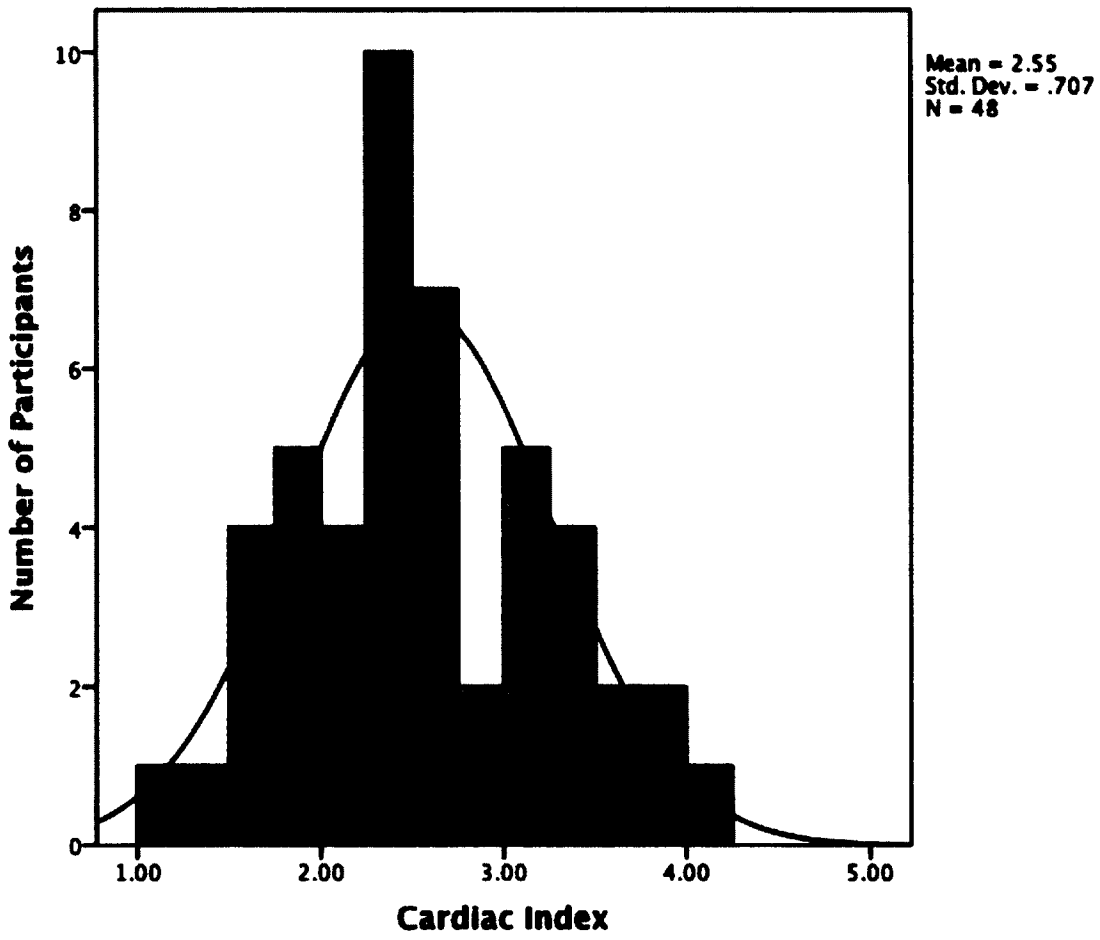

Figure 9. Cardiac index (CI).

Pulmonary vascular resistance. PVR is a measure of the right heart's afterload or mean pressure difference across the pulmonary vascular bed, divided by blood flow. Clinically this value represents resistance that the right ventricule must overcome in the pulmonary arteries and arterioles in order to eject the blood and move the blood volume forward. As the pressure in the pulmonary vasculature increase the output from the right ventricle decreases. It is usually measured in dynes/sec/cm-^{5}, with normal pressures ranging from 100 – 250 dynes/sec/cm-^{5} (Urden et al., 2010). Increased afterload remains a main measurement of heart failure in PAH (Subias et al., 2010, Humbert et al., 2004). The median PVR for this sample was 640 dynes/sec/cm-^{5} with a range of 80 to 1721.

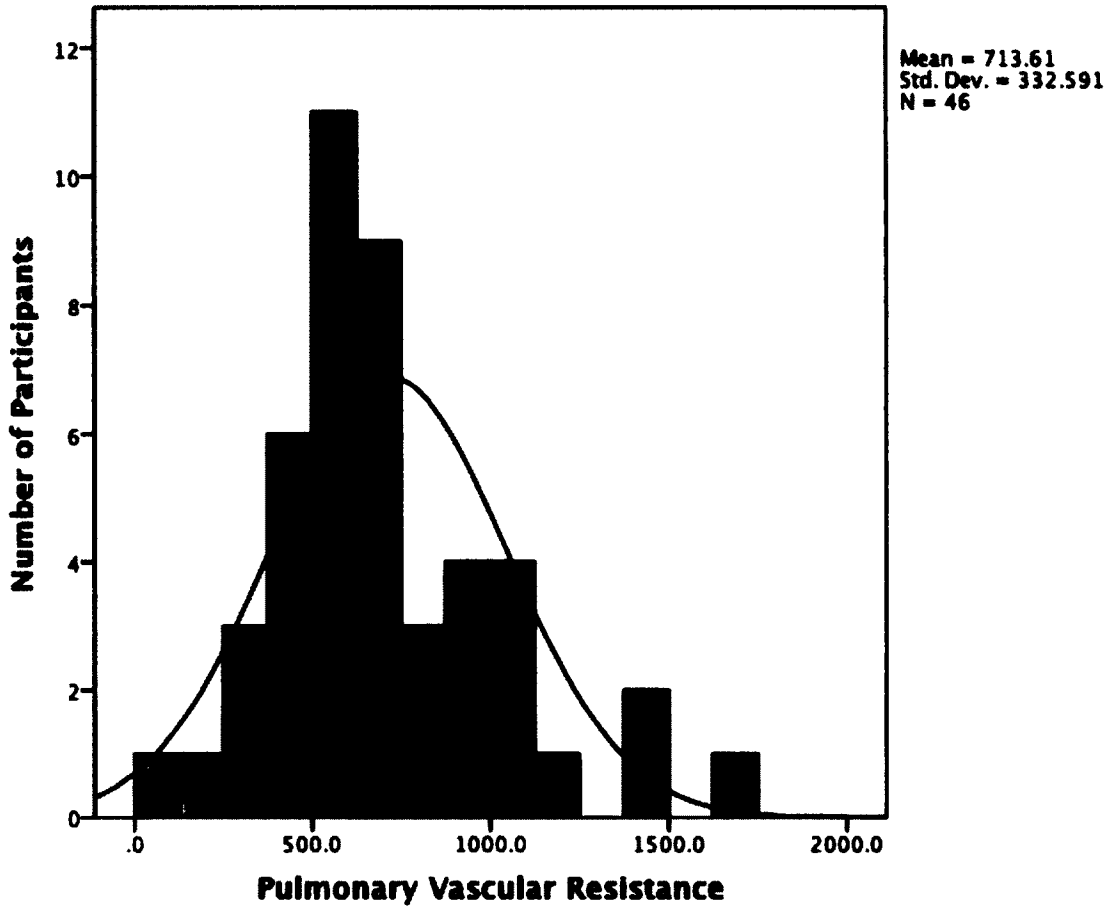

Figure 10. Pulmonary vascular resistance (PVR).

Six minute walk test. The six-minute walk test is a noninvasive and simple test measuring the distance a person is able to walk within 6 minutes. It has been found to correlate well with functional exercise capacity, disease progression, mortality, and is an established outcome in clinical trials (Guyatt et al., 1985; Humbert et al., 2004; Miyamoto et al., 2000). The general cut off for poorer prognosis is a walking distance less than 333 meters (Humbert et al., 2012). The mean distance walked in six minutes by this sample was 396 feet with a SD of 99.5.

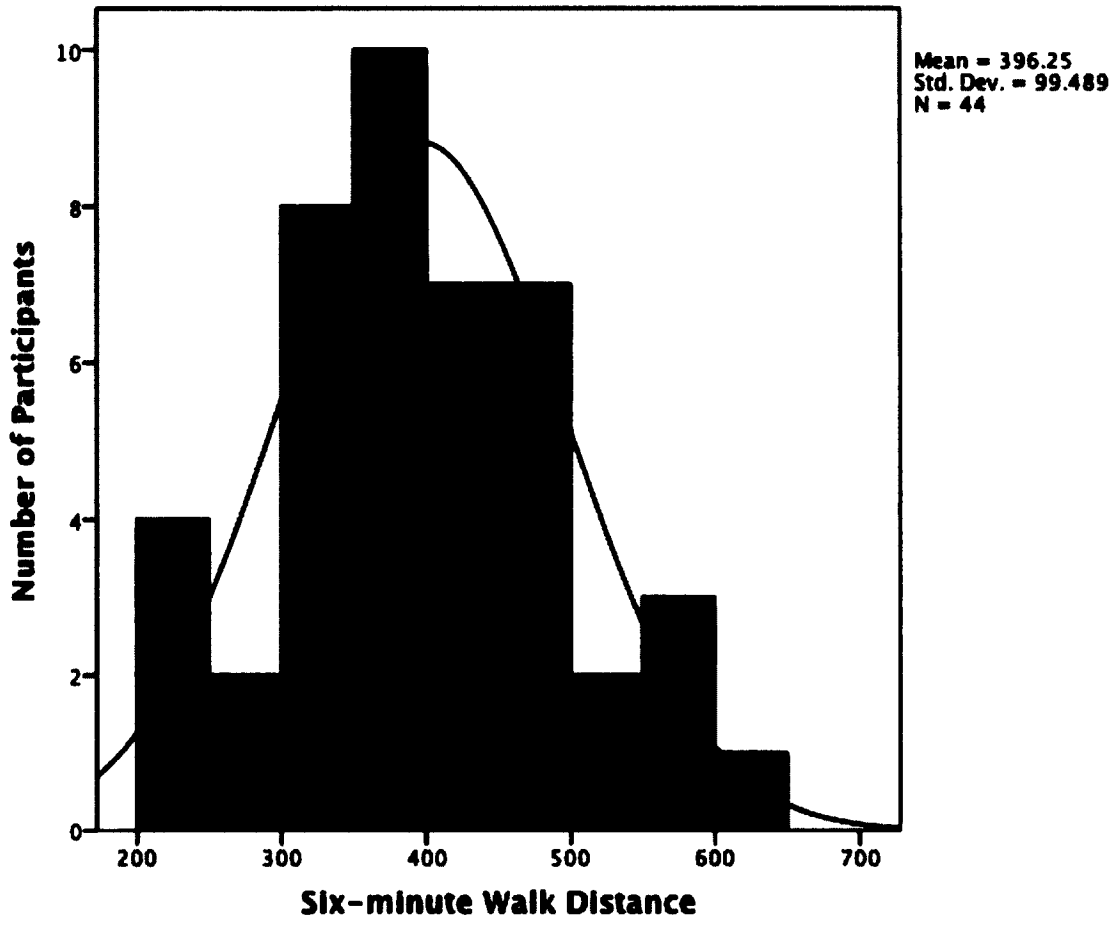

Figure 11. Six-minute walk distance (in meters).

PAH Medications. People living with PAH are often on combination medication therapy, which consists of three main groups of medication: endothelin antagonists, phosphodiesterase inhibitors, and prostanoids. In order to tease out specific symptom characteristics related to continuous intravenous prostanoid therapy the prostenoids medication group was divided into two. Flolan and Veletri are the medication delivered via continuous intravenous (IV) infusion. Ventavis and Treprostinil (subcutaneous and inhaled) are in their own category of non-intravenous (non-IV). The medication group most often prescribed is phosphodiesterase inhibitors (59%), followed by endothelin antagonists (55%), prostenoids IV (43%), and Prostenoids non-IV (39%). The specific medication most often prescribed for patients in this sample is bosentan, an endothelin antagonists.

Table 5

Pulmonary Artery Hypertension (PAH) Medications According to Medication Class

Class	***n***	**%**
Endothelin antagonists	27	55
Bosentan	22	45
Ambrisentan	6	12
Phosphodiesterase inhibitors	29	59
Tadalafil	5	10
Sildenafil	21	43
Riociguat	2	4
Prostanoids (intravenous)	21	43
Flolan	4	8
Veletri	17	35
Prostanoids (non-intravenous)	19	39
Ventavis (inhaled)	4	8
Treprostinil (subcutaneous)	7	14
Treprostinil (inhaled)	9	18

Aim 1.

The first aim of this study was to describe the occurrence and characteristics (frequency, severity and distress) of perceived symptoms using the Memorial Symptom Assessment Scale (MSAS) as reported by patients with advanced pulmonary artery hypertension. The MSAS was originally designed to measure cancer patients' perception of their symptoms (psychological, physical, and global appraisal) over the previous two weeks. This was the first time, according to the literature, this measure was used with patients with PAH. Table 12 reports the patients' perception of their symptom experience.

Total Number of Symptoms Experienced. One hundred percent of participants 100% reported some symptomology. The average number of symptoms reported was 16.0 (SD +/- 6.8), with a range from 1 to 29 symptoms. The 10 most common in order were: lack of energy (92%), shortness of breath (80%), feeling drowsy (78%), dry mouth (76%), feeling irritable (74%), numbness/tingling in hands/feet (69%), difficulty concentrating (67%), difficulty sleeping (67%), pain (63%), and cough (63%). The least reported symptoms were mouth sores (2%), weight loss (16%), constipation (18%), vomiting 918%), and changes in the way food tastes (20%).

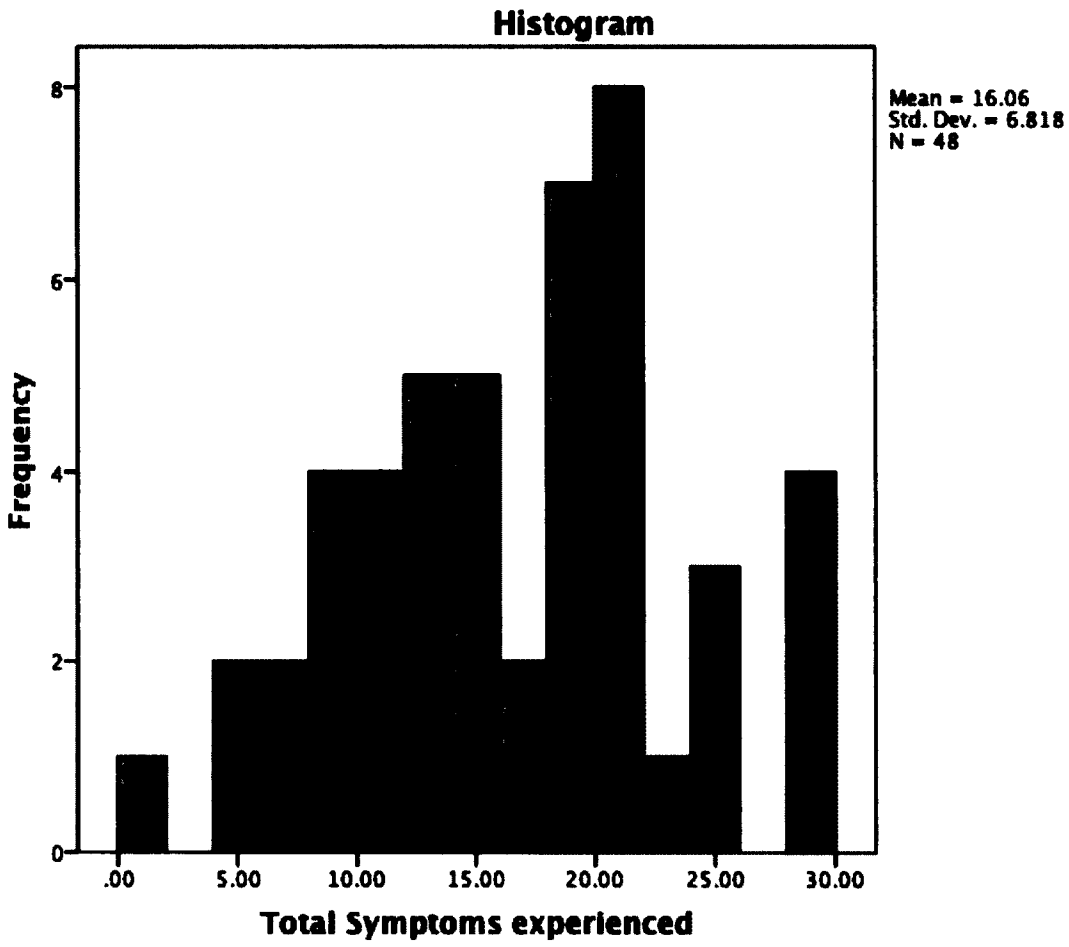

Figure 12. Total number of symptoms experienced.

The total number of symptoms experienced skewness was -.071, which is less than twice its standard error (.343). Kurtosis was -.593, which is also less than twice its standard error (.674). Thus this variable meets the assumption of normality.

Overall patients reported an average of 12 (SD +/- 5.3) out of 26 physical symptoms. The number of physical symptoms reported ranged from 1 to 22 symptoms. Most patients reported psychological symptoms (94%), with a mean number of 3.9 (SD 2.14) out of 6 possible psychological symptoms experienced. The number of psych symptoms experienced ranged from zero to 6. Participants were given the opportunity to report out on any symptoms not listed on the MSAS instrument. Of the 49 participants 9

(18%) reported other symptoms. These included jaw pain, flaky skin, dry eyes, sore throat, shaking, stomach pain, joint pain, and "feeling fed up".

The dimensions of distress, intensity and frequency provide a deeper understanding of the symptomology of the sample. The percentage of patients who reported higher scores (3 or 4 on a scale of 0-4) for these dimensions listed in Table 12. The symptoms that had the highest percentages of patients describing the frequency of their symptoms as "frequently" or "almost constantly" were, lack of energy (55%), dry mouth (43%), difficulty sleeping (39%), numbness/tingling in hands/feet (37%), and pain (35%).

The six highest symptoms that were reported as being experienced as either "severe" or "very severe" were, lack of energy (82%), shortness of breath (69%), feeling drowsy (63%), feeling irritable ((57%), difficulty sleeping (57%), and pain (57%). The top five symptoms reported a being experienced with heavy distress (i.e. "quite a bit" or "very much") include, lack of energy (44%), pain (34%), shortness of breath (32%), difficulty sleeping (31%), and diarrhea (31%).

Table 6

Prevalence and Characteristics of Symptoms and Total Memorial Symptom Assessment Scale (MSAS) Scores (N = 49)

Symptoms	*n*	Prevalence (valid %)	Heavy Frequency (%)[a]	Heavy Severity (%)[b]	Heavy Distress (%)[c]
Lack of energy	45	92	51	82	44
Shortness of breath	39	80	27	69	32
Feeling drowsy	38	78	33	63	10
Dry mouth	37	76	43	55	29
Feeling irritable	36	74	22	57	22
Numbness/tingling in hands/feet	34	69	37	49	19
Difficulty concentrating	33	67	16	31	13
Difficulty sleeping	33	67	39	57	31
Pain	31	63	35	57	34
Cough	31	63	16	33	9
Feeling nervous	30	61	20	35	8
Feeling bloated	30	61	33	39	19
Feeling sad	29	59	27	35	18
Worrying	29	59	35	53	25
Diarrhea	28	57	27	47	31
Dizziness	28	57	14	37	11
Lack of appetite	27	55	27	41	13
Nausea	25	51	22	35	19
Sweats	24	49	16	29	15
Itching	19	39	14	20	12
Difficulty swallowing	19	39	12	22	10
Swelling of arms or legs	18	37	—	31	20
Changes in skin	17	35	—	25	12
Problem urinating	16	33	8	14	6
Problems with sexual interest or activity	16	33	20	22	10
Hair loss	13	27	—	12	10
"I don't look like myself"	13	27	—	18	12
Changes in the way food tastes	11	22	—	16	6
Vomiting	10	20	4	8	6
Constipation	9	18	—	10	8
Other symptoms	9	18	—	—	—
Weight loss	8	16	—	8	0
Mouth sores	1	2	—	2	0

Note.

[a]Percentage of patients with symptom describing the frequency as "frequently" or "almost constantly."

[b]Percentage of patients with symptom describing the severity of the symptom as "moderately severe" to "very severe."

[c]Percentage of patients with symptom describing the distress associated with the symptom as "quite a bit" or "very much."

Table 7

Memorial Symptom Assessment Scale (MSAS) Scores: Total Symptoms Experienced, Total Psychological (PSYCH), and Total Physical (PHYS) Symptoms Experienced

		Total Symptoms Experienced	Total PSYCH Symptoms	Total PHYS Symptoms
N	Valid	48	48	49
	Missing	1	1	0
Mean		16.0625	3.9583	12.0816
Median		16.5000	5.0000	13.0000
SD		6.81802	2.14336	5.33790
Range		28.00	8.00	22.00
Minimum		1.00	.00	1.00
Maximum		29.00	8.00	23.00

MSAS-PSYCH Subscale. The MSAS psychological subscale consists of the following 6 psychological symptoms: difficulty concentrating, feeling sad, feeling nervous, feeling irritable, worrying, and feeling nervous. First assumptions of normality were assessed for the dependent variables of symptom burden as measured by the MSAS subscales of MSAS-PSYCH, MSAS-PSYCH, MSAS-GDI, and Total MSAS scores. PSYCH subscale skewness was .360, which is less than twice its standard error (.343). Kurtosis was -.645, which is also less than twice its standard error (.674). Thus this variable meets the assumption of normality

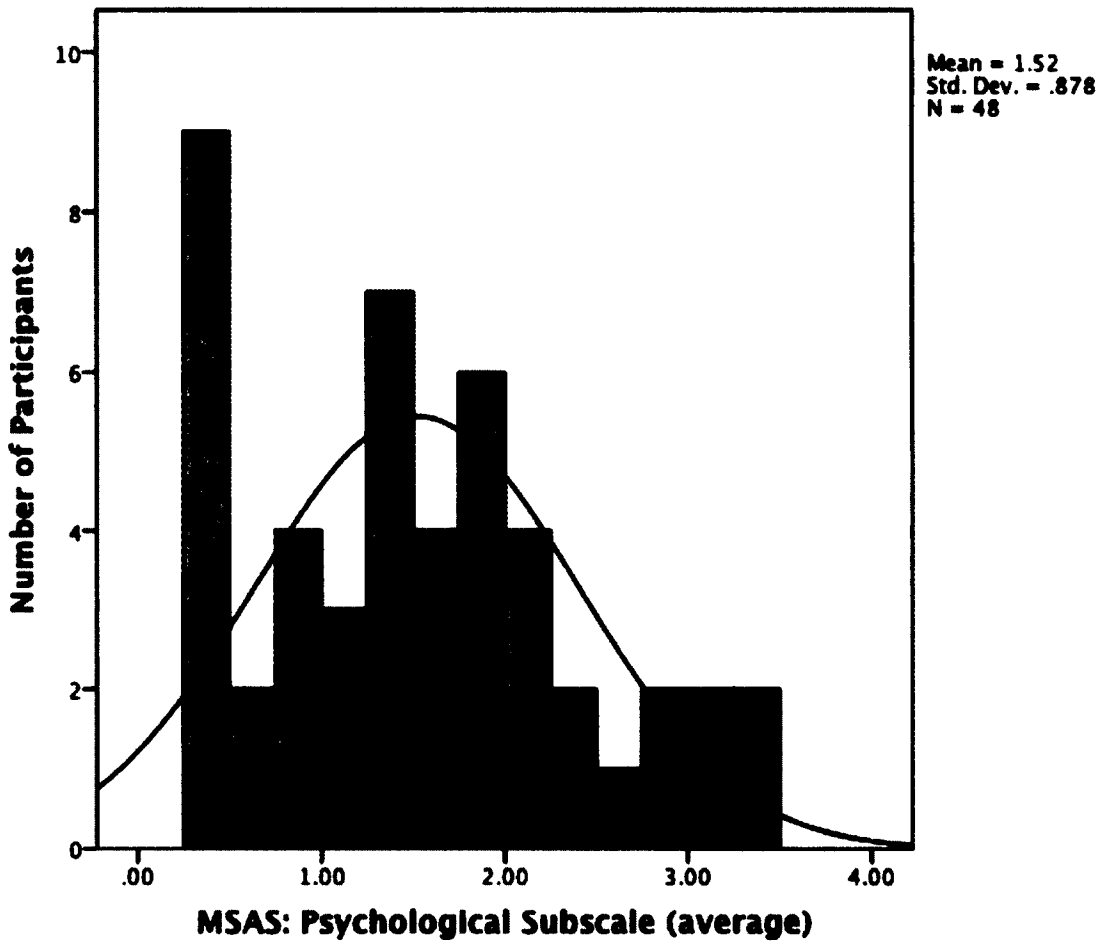

Figure 13. Memorial Symptom Assessment Scale (MSAS): Psychological (Psych) subscale average.

MSAS-PHYS Subscale. The MSAS physical subscale score is the average score of 26 physical symptoms. Physical subscale's skewness coefficient was .507, which is less than twice its standard error (.350). Kurtosis was -.0.94, which is also less than twice its standard error (.688). Thus this variable meets the assumption of normality.

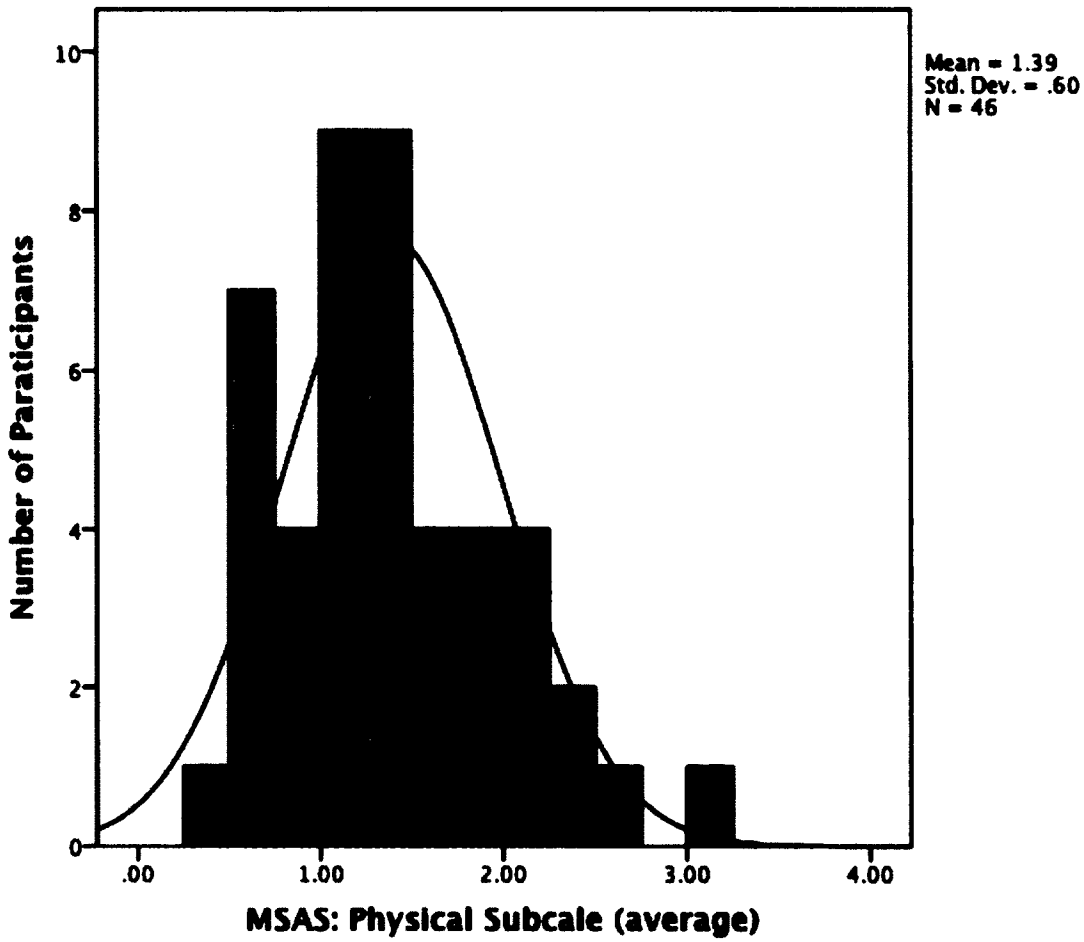

Figure 14. Memorial Symptom Assessment Scale (MSAS): Physical (PHYS) subscale score average.

MSAS-Global Distress Index (GDI) Subscale. The MSAS's global distress index (GDI) subscale is purported to be a gross measure of the perceived global symptom distress (Chang, et al., 2004; Portenoy, et al., 1994) and is comprised of the frequency scores the following four psychological symptoms: worrying, feeling sad, feeling nervous, and feeling irritable, as well as the distress scores from the following six physical symptoms: pain, lack of energy, lack of appetite, constipation, feeling drowsy, and dry mouth. The MSAS GDI subscale average score's skewness was .186, which is less than

twice its standard error of .350. Kurtosis was -.833, which is also less than twice its standard error of .688. Thus this variable meets the assumption of normality.

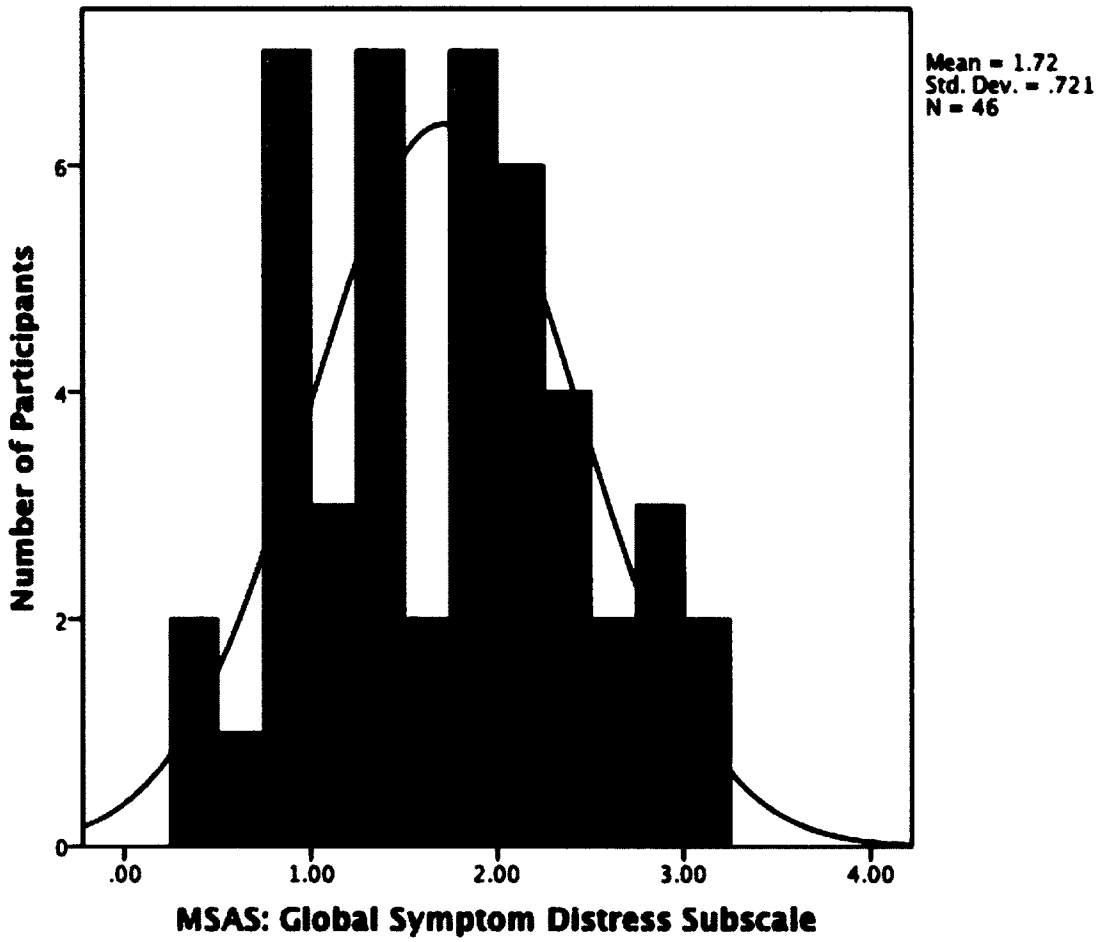

Figure 15. Memorial Symptom Assessment Scale (MSAS) Global Distress Index (GDI) subscale score average.

MSAS-Total Score scale. The MSAS total score can also be used as a measure of symptom experience. It is the average of each symptom score across the three dimensions of frequency, severity, and associated distress. The Total MSAS average score's skewness was .434, which is less than twice its standard error of .347. Kurtosis was -.067,

which is also less than twice its standard error of .681. Thus this variable meets the assumption of normality

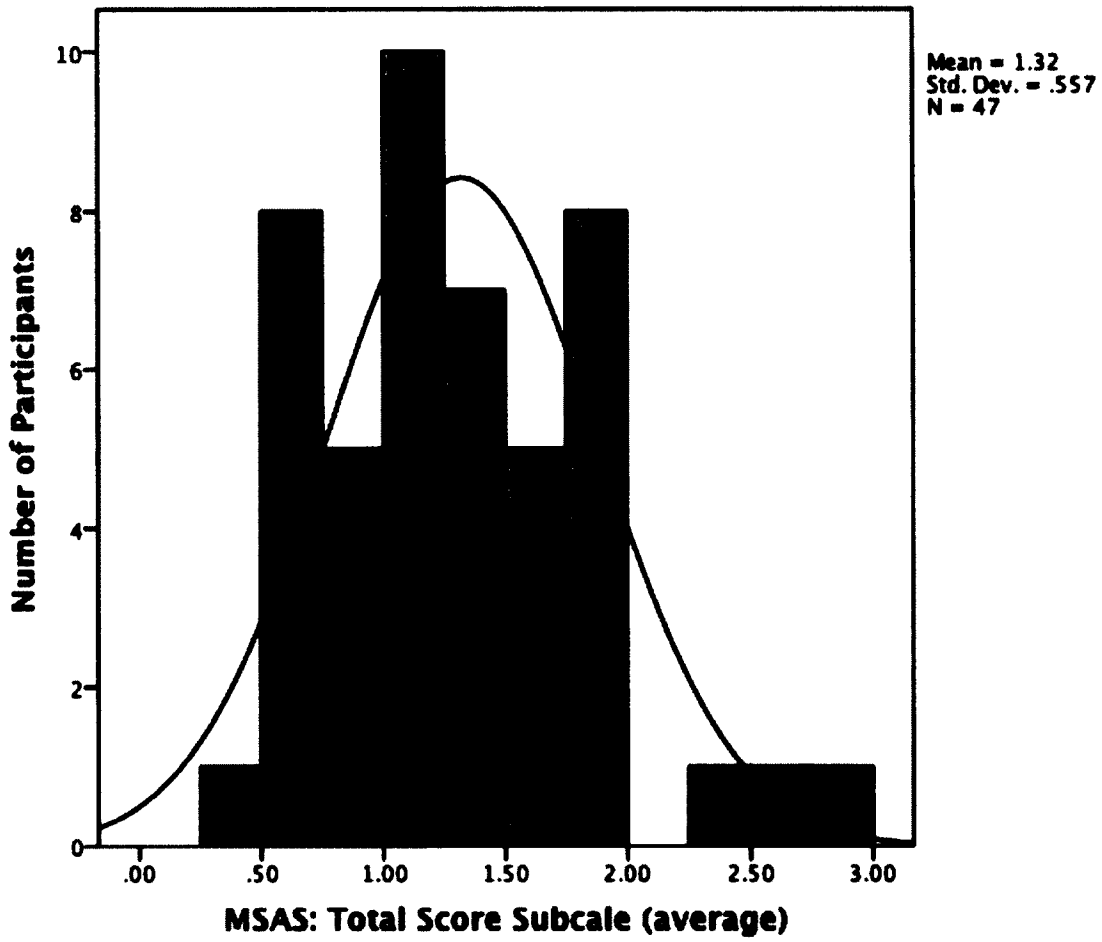

Figure 16. Memorial Symptom Assessment Scale (MSAS): Total (MSAS-Total) subscale score average.

Table 8

Memorial Symptom Assessment Scale (MSAS) Scores: Total Number of Symptoms Experienced, Psychological (PSYCH), and Physical (PHYS) Subscales, Global Distress Index (GDI), and MSAS-Total Scores.

Statistics

		Total Symptoms experienced	MSAS: PSYCH Subscale (average)	MSAS: PHYS Subscale (average)	Global Distress Index Subscale (average)	MSAS: Total Score Subscale (average)
N	Valid	48	48	46	46	47
	Missing	1	1	3	3	2
Mean		16.062	1.520	1.389	1.715	1.327
Median		16.500	1.444	1.266	1.770	1.247
Std. Deviation		6.818	.878	.600	.721	.556
Minimum		1.00	.27	.29	.48	.35
Maximum		29.00	3.32	3.01	3.16	2.78

Aim 2.

The second aim of this research was to examine the relationship between demographics (age, gender, race, education, marital status, living arrangements, and employment status), clinical characteristics (time since PAH diagnosis, medications, time on IV prostacyclin if receiving it, New York Heart Association (NYHA) functional class, right atrial pressure (RAP), cardiac index (CI), pulmonary vascular resistance (PVR), and 6 minute walk test), healthcare utilization (clinic visits, emergency department visits, and

hospitalization in the previous 6 months), and symptom burden using the Memorial Symptom Assessment Scale (MSAS) among patients with pulmonary arterial hypertension.

MSAS- GDI Subscale

The MSAS subscale GDI was correlated with all patient demographics and clinical characteristics as the main variable of symptom burden (Portenoy et al., 1994). Statistically significant positive correlations were found between GDI and education (r_{sp} = .336(44), p = .023), work status (r_{sp} = .349(44), p = .017), number of clinic visits (r_{sp} = .540(44) p = <.001). Statistically significant negative correlations were found between GDI and six-minute walk test (r = -.383(39) p = .013), and NYHA functional class (r_{sp} = .421(44) p = .004). Patients with more education, who worked less or not at all, who had more clinic visits, walked shorter distances in a six-minute walk test, and had less functionality reported higher global distress scores.

Table 9

Correlation of Memorial Symptom Assessment Scale (MSAS)-Global Distress Index Subscale With Demographics, Clinical Characteristics, and Healthcare Utilization Patterns

Measure	**Correlation Coefficients**	***p* value**
Age	r = -.043	.777
Female	r = .078	.606
Non-white	r_{sp} = .232	.121
Higher education*	r_{sp} = .336	.023 *
Not married	r_{pb} = .081	.592
Lives alone	r_{pb} = .075	.618
Not working*	r_{pb} = .349	.017 *
Time since diagnosis	r_{sp} = -.196	.191
Time on intravenous medications	r_{sp} = .033	.891
NYHA functional class*	r_{sp} = .421	.004 **
Right atrial pressure	r = .03	.847
Cardiac index	r = .055	.720
Pulmonary vascular resistance	r = -.025	.876
6-Minute walk test*	r = -.383	.013 *
> 2 clinic visits in 6 months**	r_{pb} = .466	.001 **
Emergency Department visits in 6 months, N	r = .164	.276
Hospital admissions	r = .188	.211
Diagnosis > 5 years	r_{sp} = .186	.216
> 3 years of intravenous infusion	r_{sp} = .069	.648

Note. NYHA, New York Heart Association.
r_{sp} Spearman's Rho correlation.
r_{pb} Point Biserial correlation.
r Pearson correlation.
* Statistical significant at the .05 level, ** statistical significance at the .01 level.

MSAS-PSYCH subscale.

The MSAS PSYCH subscale was correlated with demographics and clinical characteristics utilizing a Spearman's rho analysis. PSYCH subscale scores were significantly correlated with work status (r_{sp} = .325(46) p = .024) and clinic visits (r = .383(46), p = .007).

MSAS-PHYS Subscale.

The MSAS-PHYS subscale correlated with the following variables, NYHA functional class (r = .551(44), p = .001), and number of hospitalizations (r = .311(44), p = .036). It had a negative correlation with the six-minute walk distance (r = -.397(39), p = .010).

MSAS-Total Score

The Total MSAS score correlated with work status (r = .336(45), p= .021 and the number of clinic visits (r = .591(45), p = .001).

Total Number of Symptoms Experienced

The total number of symptoms experienced was correlated with the number of clinic visits in the previous six-months (r_{sp} = .392(46), p = .006), a higher functional class (r_{sp} = .376 (46), p = .008), shorter six-minute walk distance (r = .344 (41), p = .024), and being on endothelin antagonist medications (r_{bp} = .365(45), p = .012).

More than 2 clinic visits in the last 6 months correlated with heavier overall symptom burden. See Table 10.

Table 10

Association of Number of Clinic Visits, Memorial Symptom Assessment Scale (MSAS) Scores: Psychological (PSYCH), Physical (PHYS), Global Distress Index, and Total MSAS

		Three or more clinic visits in previous 6 months
Three or more clinic visits in previous 6 months	Pearson correlation Sig. (2-tailed) *N*	1 49
MSAS: PSYCH Scale (average)	Pearson correlation Sig. (2-tailed) *N*	.304* .035 48
MSAS: PHYS Scale (average)	Pearson correlation Sig. (2-tailed) *N*	.496** .000 46
Global Distress Index (average)	Pearson correlation Sig. (2-tailed) *N*	.466** .001 46
MSAS: Total Score Scale (average)	Pearson correlation Sig. (2-tailed) *N*	.428** .003 47
MSAS: Total Number of Symptoms Experienced	Pearson correlation Sig. (2-tailed) *N*	.432** .002 48

Note. *Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

Dummy Coding. Point-Biserial correlation analysis was conducted after collapsing and dummy coding the following variables, education into college versus no college, race into white versus non white, marriage status into married versus not married and work status into working versus not working. The only statistically significant correlation found with GDI scores was work status. Work status was significantly related to GDI scores, (r_{pb} = .401(44) p = .006). Patients who did not work reported higher symptom burden. For the PHYS subscale the only significant correlation was also with work status (r_{pb} = .432(44) p = .003). The pattern was similar for the Total MSAS scores (r = .395(45), p = .006). Patients who did not work reported higher global symptom burden, higher psychological and physical symptoms as well as total score for the MSAS.

New York Heart Association (NYHA) Functional Class. Due to the lower number of participant classified as lass IV (n = 4) this variable was dummy coded into a dichotomous variable for analysis. Point Biserial correlation was computed (Table 17). Patients with a higher functional ability (FC II) had lower scores on the MSAS-PHYS, and GDI subscales as well as fewer average symptoms as compared to patients in either FC II or IV.

Table 11

Associations Between Memorial Symptom Assessment Scale (MSAS) Scores: Physical (PHYS), Global Distress Index, Total MSAS, Psychological (PSYCH), and NYHA Functional Classes III & IV

		NYHA Functional Class III & IV
MSAS: PHYS Scale (average)	Pearson correlation	.509**
	Sig. (2-tailed)	.000
	N	46
Global Distress Index (average)	Pearson correlation	.377**
	Sig. (2-tailed)	.010
	N	46
Total Symptoms experienced	Pearson correlation	.362*
	Sig. (2-tailed)	.012
	N	48
MSAS: PSYCH Scale (average)	Pearson correlation	.212
	Sig. (2-tailed)	.148
	N	48

Note. NYHA, New York Heart Association. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

Independent t-tests were conducted with the recoded binary functional class. Patients in Class II (n= 21) versus patients in class III and IV (n=25). Functional class II participants had lower mean (SD) number of total symptoms M= 13.41 (5.93) compared to class III and IV (M= 18.31 (SD = 6.81), t(46) = -2.63, p = .012). Patients in FC II also had lower average MSAS-PHYS subscale scores (M = 1.06 (SD = .423) as compared to those in FC III and IV (M= 1.67 SD= .592), t(44) = -3.919, p = .001). Patients in FC II

also had lower average MSAS_GDI subscale scores (M = 1.42, (SD = .619) as compared to those in FC III and IV (M= 1.96 (SD= .718), t(44) = -2.703, p = .010). There was no significant difference between the FC for average MSAS-PSYCH subscale sores. Overall, patients with higher function (i.e. lower FC) experienced less symptom distress.

Comparison of Means. Several demographic, clinical and healthcare utilization variables were recoded into dichotomous dummy variable for further analysis using independent t-test or Mann-Whitney U tests as necessary. Participants who were working, either part or full time, reported significantly lower GDI scores (M= 1.13, SD = .520) than people not working (M= 1.85, SD = .696) (t(44) = -2.90, p = .006). Working participants also reported lower PHYS scores (M =0.869 (SD = .347) versus non working (M = 1.51 (SD = .582), t(44) = -3.18, p = .003). Working participants again reported lower PSYCH subscale scores (M = 1.287 (SD = .798) compared to non workers (M = 1.82 (SD = .9025) t(44) = -3.788, p = .035). Furthermore, patients who made three or more pulmonary hypertension clinic visits within the previous six month had significantly higher GDI scores (M= 2.09, SD = .615) compared to patients who had one or two clinic visits (M= 1.42, SD =.66, t(44) = -3.49, p = .001). This pattern was similar to PHYS subscale scores (M = 1.13 (SD = .48) versus M = 1.72 (.57) t(44) = -3.788, p < .001), and PSYCH subscale scores (M = 1.29 (SD = .79) versus 1.82(SD = .90) t(46) = -2.17, p = .035). There was no significant difference between the GDI, PSYCH, or PHYS subscale scores in the following binary categories: white versus non-white, married versus not married, college versus no college, living alone versus with others, less than five years since diagnosis versus five or more years, and less than 3 years receiving continuous infusion versus thee or more.

PAH Medications Analyses. Bivariate correlations were completed with each MSAS subscale PAH medications according to larger grouping and individual medications. There were no significant correlations between the MSAS GDI subscale across all medications. The MSAS PHYS subscale had a significant inverse correlation with ambrisentan r_{pb} = -.347(44) p = .018. The MSAS-Total subscale had a significant direct correlation with ventavis (r_{pb} = .310(46) p = .032 and an approach to significant correlation with Flolan (r_{pb} = .278(48) p = .055). The MSAS PSYCH subscale has a correlation that approached significance with the medication ventavis (r_{pb} = .276(46) *p* = .057). Patients that were on ambrisentan had associated lower physical distress scores, while patients on ventavis had associated higher number of symptoms, but only approached significant correlation with higher psychological distress scores. Patients on Flolan also had a correlation that approached significance with a higher number of total symptoms.

Point Biserial correlation was conducted on the larger grouping of PAH medications such as endothelin antagonists, phosphodiesterase inhibitors, intravenous (IV) prostenoids, and non-intravenous (non-IV) prostenoids. Endothelin antagonists had a significant negative correlation between the MSAS-PHYS (r_{pb} = -.302(43) p = .044), MSAS-GDI (r_{pb} = -297(43), p = .048), and MSAS-Total subscales (r_{pb} = -.373(45), p = .010). Patients receiving endothelin antagonist medications for management of PAH had an associated lower number of total symptoms, lower physical distress, and overall distress scores.

Independent t-tests were run with the four larger groupings of PAH medications. Patients receiving endothelin antagonists reported a statistically lower number of

symptoms experienced (M = 13.73, SD = 6.98) as compared to patients not receiving this type of medication (M= 18.71, SD = 5.71, t(45) = 2.634, p = .012). Patients receiving endothelin antagonists reported significantly lower average GDI subscale scores, M = 1.52, (SD= .657) versus 1.92 (SD = .758) lower PSYCH subscale average scores M = 1.32 (SD = .86), versus 1.74, (SD = .87) or lower PHYS subscale average scores M = 1.24 (SD = .63) versus 1.55 (SD= .53) though non were statistically significant.

Medication usage was then correlated with healthcare utilization. Point Biserial correlation revealed statistical association between patients receiving intravenous (IV) prostanoid therapy and the number of emergency department (ED) visits in the previous 6 months (r_{pb} = .493(47), p < .001), as well as number of hospitalization in the previous six months (r_{pb} = .288(47), p = .044). Mann-Whiteny U testing was then performed on these two significant findings due to not meeting homogeneity or normality assumptions. The distribution of the number of ED visits was not the same across the category of receiving IV prostanoid therapy (p <.001). The distribution of the number of hospital admissions was not the same across the category of receiving IV prostanoid therapy (p = .049). Patients on IV prostanoid therapy had higher ED visits and hospitalizations.

Summary

This chapter presented the results of the data analysis in three sections, according to stated aims. First, was a description of the sample demographics, clinical characteristics and healthcare utilization patterns. Second, descriptive findings of the MSAS and its subscales were discussed. Third, the relationships between demographics, clinical characteristics, healthcare utilization, and symptom burden variables were

discussed. Patients living with PAH reported heavy symptom burden that was associated with several variables, most notably not working and more than two pulmonary clinic visits in the previous 6 months.

CHAPTR V

Results Summary, Conclusions, Implications and Recommendations

Overview

This study employed the Revised Symptom Management Model (Dodd et al., 2001) as its theoretical framework to study symptom burden (frequency, distress, intensity) and overall symptom distress among participants (n = 49) diagnosed with pulmonary arterial hypertension using the Memorial Symptom Assessment Scale (MSAS) (Portenoy et al., 1994) as the multidimensional instrument to measure the symptom burden experience Symptom assessment is important because symptoms directly influence patient distress, QOL, survival, and family experience during the disease trajectory. In this chapter the meaning and significance of the study findings, along with comparisons in the literature will be presented. The strengths and limitations of the study are also reviewed. Finally, the implications of the study findings and directions for future research are outlined.

Symptom Burden Findings.

This is the first study utilizing the MSAS in a PAH cohort to assess symptom burden and associated relationships with sociodemographics, clinical variables and healthcare utilization patterns. Of the participants (n = 49), 100% reported some

symptomology. The average number of symptoms reported was 16.0 (SD +/- 6.8), with a range from 1 to 29 symptoms. The 10 most common in order were, lack of energy (92%), shortness of breath (80%), feeling drowsy (78%), dry mouth (76%), feeling irritable (74%), numbness/tingling in hands/feet (69%), difficulty concentrating (67%), difficulty sleeping (67%), pain (63%), and cough (63%). The least reported symptoms were mouth sores (2%), weight loss (16%), constipation (18%), vomiting (18%), and changes in the way food tastes (20%).

The vast majority of the PAH sample reported lack of energy (92%). Of these 82% reported experiencing it with heavy severity, yet less than half (44%) reported heavy distress associated with experiencing lack of energy. Most of the patients in this study felt they were experiencing severe energy loss, yet a little less than half felt this caused them high distress levels. This may reflect the sample's acceptance of living with a heavy symptom burden. Previous qualitative work with PAH patients receiving continuous intravenous epoprostenol therapy discovered themes of "figuring it out" and "giving life" (Hall, McBean, & Purden, 2010). Almost half of this population (43%) was receiving IV prostanoid medical therapy. Other qualitative studies with people living with PAH revealed similar themes entitled "doing what I have to do," "resuming life's activities" (Flattery et al., 2004), and "redefining life" (McDonough, Matura, & Carroll, 2011). This may be an example of patients learning to live within the limitations of their disease, its treatment, and appreciate what life still had to offer them.

Lack of energy is a vague symptom that can be misconstrued by those living with or in proximity to a person with PAH. Previous qualitative studies indicated patients felt their lack of energy was misconstrued as being lazy (Ferrari et al., 2013; Guillevin et al.,

2013). This sometimes created distance between the patient and people around them. A large study of people living with PAH in Europe (n= 326) revealed 26% of participants felt misunderstood and 22% felt worthless (Guillevin et al., 2013). Caregivers and providers need to be aware of and sensitive to the profound nature of the symptom, lack of energy, to help mitigate further emotional and physical isolation of patients living with PAH.

The six symptoms that were reported with heavy severity (i.e. reported as being experienced as either "severe" or "very severe") were, lack of energy (82%), shortness of breath (69%), feeling drowsy (63%), feeling irritable (57%), difficulty sleeping (57%), and pain (57%). The top five symptoms reported with heavy distress (i.e. describing the distress as "quite a bit" or "very much") included, lack of energy (44%), pain (34%), shortness of breath, difficulty sleeping (31%), and diarrhea (31%). These finding may encourage providers to dive deeper in to their patients' symptomology. Knowing the symptoms that are associated with higher levels of distress can help to prioritize symptom assessment during concise clinic visits. Symptom experts such as palliative care providers can help to mitigate symptoms, for instance pain, dyspnea, diarrhea and problems sleeping, which had a higher occurrence of patients experiencing them at higher levels of (i.e. heavy) severity in this study.

Recent studies measuring symptom burden with the MSAS tool in other cardiopulmonary disease states reported a lower median number of symptoms, 9 (range 0-26) in patients with congestive heart failure (CHF) (Blinderman et al., 2008) and 10.5 (range 0-25) in patients with chronic obstructive pulmonary disease (COPD) (Blinderman et al., 2009), as compared to patients with PAH 16.5 (range 1-29). The three most

prevalent symptoms shared among the three disease processes were, lack of energy, SOB, and dry mouth. Overall a greater percentage of PAH patients experienced symptoms as compared to CHF and COPD (Table 18). This underscores the heavy symptom burden of living with PAH.

Table 12
Prevalence of Symptoms in Pulmonary Artery Hypertension (PAH), Chronic Heart Failure (CHF), and Chronic Obstructive Pulmonary Disease (COPD)

PAH (N=49)	**CHF[a] (N=103)**	**COPD[b] (N=100)**
Lack of energy 92%	Lack of energy 66%	Shortness of breath 94%
Shortness of breath 80%	Dry mouth 62%	Lack of energy 71%
Feeling drowsy 78%	Shortness of breath 56%	Dry mouth 60%
Dry mouth 76%	Feeling drowsy 52%	Cough 56%
Feeling irritable 74%	Tingling 49%	Worrying 51%

Note. [a] (Blinderman et al., 2008). [b] (Blinderman et al., 2009)

The MSAS subscales revealed moderate to severe distress in the overall sample with wide variation in each subscale. The median (range) for the MSAS GDI 1.77 (.48, 3.16), and medians (ranges) for the MSAS-Total, MSAS PSYCH, and MSAS PHYS were 1.24 (.35-2.78), 1.44 (.27-3.32), and 1.26 (.29-3.01) respectively. Again, these scores indicate a distinctively higher symptom burden in comparison to other cardiopulmonary diseases. For example the MSAS GDI median (ranges) for patients with CHF and COPD were .9 (0, 2.80) and .68 (0, 1.90) respectively. The sample (n = 103) for the CHF study included patients with a NYHA functional class (FC) of III or IV. This PAH study consisted of almost half the patients being class II (47%) and only 8.2% in

class IV. Despite possessing better functional status, PAH patients reported distinctively higher symptom burden across the MSAS indices (Table 19). This finding could also be indicative of mis-categorizing of PAH patient's functional status, which supports the findings from Taichman et al. (2009) study, but such a large percentage (47%) of patients being seen by a diverse group of physicians being incorrectly categorized seems unlikely. Taken as a whole these finding underscore the particularly heavy symptom burden experienced by patient living with advanced PAH.

Table 13
Descriptive Statistics for Memorial Symptom Assessment Scale (MSAS) Subscale Scores in Pulmonary Artery Hypertension (PAH), Chronic Heart Failure (CHF), and Chronic Obstructive Pulmonary Disease (COPD)

		Disease Type		
		PAH (n = 49)	**CHF**[a] (n = 103)	**COPD**[b] (n = 100)
Measure	Possible range of scores	Median (min, max)		
MSAS symptoms per patient, *n*	1–33	16.5 (1,29)	9 (0,26)	10.5 (0, 25)
MSAS-GDI	0–4	1.77 (.48, 3.16),	0.90 (0, 2.80)	0.68 (0, 1.90)
MSAS-PHYS	0–4	1.26 (.29-3.01)	0.62 (0,3.22)	0.78 (0, 2.97)
MSAS-PSYCH	0–4	1.44 (.27-3.32),	0.63 (0, 2.77)	0.56 (0, 2.02)
MSAS-Total	0–4	1.24 (.35-2.78)	0.52 (0, 2.13)	0.75 (0, 2.80)

Note. PHYS, physical symptom distress; PSYCH, psychological symptom distress; GDI, global distress index. [a] (Blinderman et al., 2008); [b] (Blinderman et al., 2009)

Correlational Findings

The global distress index subscale scores were significantly correlated with the following variables: education, work status, number of pulmonary clinic visits in the previous six months, six minute walk distance, and had less functionality (i.e. higher

NYHA functional class). The physical subscale scores were significantly correlated with the following variables: time since diagnosis, number of pulmonary clinic visits in the previous six months, hospital admissions in the previous six months, six minute walk distance, and NYHA functional class. The psychological subscale scores were significantly correlated with work status and number of pulmonary clinic visits in the previous six months. The MSAS-Total subscale scores were significantly correlated with work status and clinic visits. Finally, the total number of symptoms experienced per patient was significantly correlated with work status, functional class, and number of clinic visits. No significant correlation was found between pulmonary hemodynamic parameters. This supports the findings of previous studies showing low correlation with how patients feel and function in their lives with hemodynamics (Cenedese, et al., 2006; Chua, et al., 2006; Taichman, et al., 2005).

Patients who did not work had significant correlation with overall heavier symptom burden. Specifically they reported higher global distress, physical, psychological, total scores, as well as total number of symptoms experienced. Employment status may be an important aspect of assessing patients' symptom burden experience. People with lower symptom burden have better physical ability to work. The job itself may be a distractor from the symptom experience. Further studies into the type and amount of employment may be needed to better understand the relationship.

Several demographic, clinical, and healthcare utilization variables were recoded into dichotomous dummy variable for further analysis. Participants working, either part or full time, reported lower GDI ($p = .006$), PHYS ($p = .003$), and PSYCH ($p = .035$) subscale scores. Furthermore, patients who made more than two pulmonary hypertension

clinic visits within the previous six months had significantly higher GDI ($p = .001$), PHYS ($p = <.001$), and PSYCH ($p = .035$) subscale scores. There was no significant difference between the GDI, PSYCH, or PHYS subscale scores in the following binary categories: white versus non-white, married versus not married, college versus no college, living alone versus with others, less than five years since diagnosis versus five or more years, and less than 3 years receiving continuous infusion versus thee or more. Length of time living with the disease or length of time receiving continuous intravenous infusion was not associated with a heavier symptom burden. Healthcare providers need to be aware that work status and frequency of clinic visits may be indicators for patients at higher risk for heavy symptom burden in need of increased supportive services.

As expected patients with higher function (lower NYHA functional class) experienced less symptom distress. Independent t-tests run with the recoded binary functional class (FC II versus FC III and IV) revealed patients in FC II had lower mean number of total symptoms experienced ($p = .012$), lower average MSAS-PHYS subscale scores ($p = .001$), and lower MSAS-GDI subscale scores ($p = .010$). There was no significant difference between the FC for average MSAS-PSYCH subscale sores. Overall, patients with higher function experienced less symptom distress. These findings identify FC III and IV patients as reporting significantly higher symptom distress and should encourage healthcare providers to consider all FC III and IV PAH patients to be candidates for integrating palliative care into their standard care earlier in the disease trajectory.

PAH Medication Findings. Bivariate correlations were run with the MSAS subscales and PAH medications according to individual medications, as well as larger grouping of type (endothelin antagonist, phosphodiesterase inhibitors, IV prostanoid and non IV prostanoid). There was no significant correlation with the MSAS GDI subscale across all medications. The MSAS PHYS subscale had a significant negative correlation with ambrisentan (r_{pb} = -.347(44) p = .018). The MSAS-Total subscale had a significant positive correlation with ventavis (r_{pb} = .310(46) p = .032, and approached significance with Flolan (r_{pb} = .278(48) p = .055). The MSAS PSYCH subscale has a correlation that approached significance with the medication ventavis (r_{pb} = .276(46) p = .057). Patients who were on ambrisentan, an endothelin antagonist, had associated lower physical distress scores, while patients on ventavis, an inhaled prostanoid had associated higher number of symptoms, and approached a significant correlation with higher psychological distress scores (r_{pb} = .276(46) p = .057). Patients on Flolan also had a correlation that approached significance with a higher number of total symptoms (r_{pb} = .278(48) p = .055).

Point Biserial correlation was conducted on the larger four groups of PAH medications such as endothelin antagonists, phosphodiesterase inhibitors, IV prostenoids, and non-IV prostenoids. Endothelin antagonists had significant inverse correlations with the MSAS-PHYS (r_{pb} = -.302(43) p = .044), MSAS-GDI (r_{pb} = -.297(43), p = .048), and MSAS-Total subscale (r_{pb} = -.373(45), p = .010). Unexpectedly, patient receiving endothelin antagonist medications for management of the PAH had an associated lower number of total symptoms, lower physical distress, and overall distress scores. One possibility is the association between endothelin antagonists medication and lower levels

of biomarkers such as Interleukin 6 in systemic sclerosis (Bellisai, et al., 2010), which causes symptoms such as fatigue.

Patients receiving endothelin antagonists reported a statistically significant lower number of symptoms experienced. They also reported lower GDI, PSYCH, and PHYS subscales average scores though none were significant. Patients receiving endothelin antagonists such as bosentan and ambrisentan experienced lower symptom burden compared to patients not receiving this group of medications.

Patients receiving ambrisentan medication had lower physical distress scores, while patients on ventavis reported a higher number of symptoms, and approached a statistically significant correlation with higher psychological distress scores. Patients on Flolan had a correlation that approached significance with a higher number of total symptoms. Healthcare providers need to be aware of possible heavier symptom burden for patient using ventavis. This inhaled medication may need to be delivered up to 9 times a day with each dosing requiring five to ten minutes to deliver. Increased education and support may be required for these patients. Further studies into possible non-adherence being a causative factor needs to be done.

Analyses of relationships between PAH medication use and healthcare utilization revealed significant findings. Patients on IV prostanoid therapy had higher ED visits and hospitalizations, mostly related to central-line occlusion, infection or fluid overload. These finding support the need for increased support for patients receiving continuous IV therapy. The distribution of the number of ED visits was not the same across the category of receiving IV prostanoid therapy ($p < .001$). The distribution of the number of hospital admissions was not the same across the category of receiving IV prostanoid therapy (p

= .049). Patients on IV prostanoid therapy had a higher number of ED visits and hospitalizations.

Research Strengths and Limitations

This study is the first study to use the MSAS for symptom assessment in patients diagnosed with PAH. Presently the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) (Gomberg-Maitland et al., 2008) is the measure used in clinical trials for measurement of health related quality of life (HRQOL) in persons living with all types of pulmonary hypertension, not just PAH. This instrument was shown to have reliable and valid scores yet it does not allow for answers to be on a continuum and may miss out on more detailed information. Respondents mostly may choose only dichotomous answer choices; true/false or yes/no answers. Previous studies in PAH have pointed out the shortcomings of the (CAMPHOR) to adequately assess symptomology (Matura et al., 2014). The MSAS provides a more in-depth understanding of the symptom experience and its dimensions of severity. There is also no measure of the associated distress from the symptoms, which is a vital aspect of the Revised Symptom Management Model (Dodd et al., 2001).

Limitations. This study has several limitations. First the sample size was less than the 85 calculated with the power analysis and was a convenience sample from a single site. Institution-based differences in treatment or patient population may limit this study's generalizability. The predominance of females (90%) may have also diminished the generalizability. Similar studies with larger PAH patient samples (n =326 and n = 191) had 75% and 85% female participants respectively (Guillevin et al., 2013; Matura et al.,

2014a), as well as the REVEAL registry which also shows similarities in the therapeutic management of this cohort with a national PAH registry (Barst, et al., 2013).

The MSAS scores have not been validated for patients with PAH. One of the symptoms in the GDI subscale is constipation. In patients with PAH, diarrhea is a common (57%) symptom with 47% reporting high severity in this sample. Constipation was reported by only 18% of the sample and only 10% reported the constipation being very severe. This underscores the importance of using a psychometrically tested, disease specific tool for measuring symptom burden in patients living with PAH.

Healthcare utilization patterns looked at only the incidences directly related to patients' PAH diagnosis or treatment. Measuring all clinic visits, emergency room visits and hospitalization may have provided a deeper picture of this sample's healthcare needs and utilization. This study did not measure comorbidities, which may have elucidated relationships between certain comorbidities and heavier symptom burden. A more indepth look at healthcare utilization with comorbidities in PAH would be important information to have in identifying patients in need of increased support.

Conclusions

Patients living with PAH experience distinctively heavier symptom burden in the occurrence, frequency, intensity, and distress associated with their symptoms overall as compared to those with other cardiopulmonary disease, such as CHF and COPD. A general sense of profound lethargy was prevalent in this sample as measured by the high occurrence and severity reported with symptoms such as lack of energy, shortness of breath, difficulty sleeping, and feeling drowsy. Caregivers and providers need to be aware of the intense nature of fatigue in patients living with PAH. Patients may learn to

live within the limitations of the disease and its treatment, thus making overt displays of symptomatology subtler and more difficult to assess and appreciate. Better education to caregivers and families make help to prevent misunderstanding and improve family cohesiveness.

Close to half of participants (43%) had three or more clinic visits in the previous six months. This finding was highly related with all measure of symptom burden. Higher clinic visits along with non-working status and NYHA FC III and IV were all better clinical indicators of heavy symptom burden than hemodynamic such as right atrial pressure, cardiac index, and pulmonary vascular resistance. This supports the Revised Symptom Management Model (Dodd, et al., 2001) purported relationship between functional status, which is considered a symptom outcome, increased clinic visits which could be considered a symptom management strategy, and work status, which is a representation of the person and their environment.

Pulmonary arterial hypertension may be considered an orphan disease but it posses heavy symptom burden for the patient and heavy healthcare utilization for the healthcare system. Forty three percent of this sample (N = 21) were receiving continuous IV therapy. These patients had significantly higher emergency department visits and hospitalizations. The sickest 10% of the US population accounts for more than half of its healthcare expenditures (Zuvekas & Cohen, 2007). Earlier identification of patients living with PAH experiencing heavy symptom burden can benefit the patient and their family foremost, but may also help to achieve the Institute of Healthcare Improvement's (IHI) triple aim of: improving patients' experiences of care (including quality and satisfaction),

improving the health of populations, and reducing the per capita cost of healthcare (Berwick, Nolan, & Whittington, 2008).

Patients receiving endothelin antagonist medications experience a lower number of total symptoms and less psychological distress. Patients receiving an inhaled prostanoid (ventavis) reported a higher number of symptoms. Patients on IV prostanoid (Flolan) had a correlation that approached significance with a higher number of total symptoms. Patients receiving prostenoids whether inhaled or IV require a deeper assessment of their symptom burden to identify the need for increased supportive services.

These findings underscore the heavy symptom burden experienced by patients living with PAH. Once patients are classified as NYHA FC III or higher they could benefit from integration of palliative care into their standard care. According to the Center to Advance Palliative Care (CAPC) (2014) palliative care is a medical subspecialty providing patient relief from the symptoms, pain, and stress of serious illness with the goal of improving quality of life for both the patient and the caregiver. Integration of palliative care has been shown to increase quality of life, decrease depression and aggressive care at end-of-life, as well as increase life expectancy in other diseases (Temel, et al., 2010). It is time to study the impact palliative care can have in the lives of people living with PAH.

Implications for Nursing Practice

Nurses caring for patients with PAH need to advocate for improved palliative care integration earlier in the disease trajectory. People in functional class III or higher are at greater need of the supportive services palliative care provides. Palliative care provides

patient and family centered care by having discussions about goals of care and then working to ensure the care provided is aligned with the established goals. Bedside nurses can advocate for palliative care consults for PAH patients in NHYA FC III or IV by talking with the pulmonary team and educating them about the ways palliative care can improve the patient and caregivers quality of life.

Future Research and Policy

A reliable and validated instrument to measure symptom burden in PAH is still needed. This feasibility study has underscored the association of heavy symptom burden of people diagnosed with PAH with higher levels of medical support and /or in higher functional classes II or IV. Larger studies to elucidate strong predictors of heavy symptom burden are needed to better identify patients in need of palliative care earlier in the disease trajectory of PAH are needed.

The large International PAH Patient and Carer Survey (n = 362) made recommendations for a more multidisciplinary health care team to provide the comprehensive care PAH patients require for optimal management and treatment of their disease (Guillevin et al., 2013). A large, multi-center, randomized controlled trial measuring disease progression, QOL (of patients and caregivers), and healthcare utilization metrics comparing integration of an interdisciplinary palliative care team into standard care for functional class III or higher patients, versus standard PAH care may provide the empirical evidence needed to change care for the better, on a larger scale.

This is the first study to describe associations between symptom burden and healthcare utilization more research is needed to further understand and mitigate the heavy symptom burden of PAH.

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APPENDIX A

University of San Diego Institutional Review Board Approved Consent

#130873

University of California, San Diego
Consent to Act as a Research Subject

Symptom Burden in Pulmonary Arterial Hypertension

Michael Madani MD and Catherina Madani, RN are conducting a research study to find out more about the impact of symptom burden in advanced pulmonary arterial hypertension patients. Symptom Burden is another way of saying, what effect your pulmonary arterial hypertension symptoms are having on you and your life. You have been asked to participate in this study because you are identified as having pulmonary arterial hypertension and coming to pulmonary clinic at UCSD. There will be approximately 150 participants. The purpose of this study is to learn more about living with the symptoms of pulmonary arterial hypertension.

If you agree to be in this study, the following will happen to you:
You will be asked to complete a packet of questionnaires on personal and clinical information about yourself, a 20 questionnaire about the your social support called the Medical Outcomes Study-Social Support Scale (MOS-SS), and a 32 questionaire about your symptom experience called the Memorial Symptom Assessment Scale (MSAS). The estimated time to compete the surveys is 10 minutes. Catherina Madani will review your chart for medical markers of your pulmonary arterial hypertension condition, such as your right heart function.

Participation in this study may involve some added risks or discomforts. These include: the possibility of an increased awareness of your own symptom burden which may result in anxiety or distress. Information about the local and national Pulmonary Hypertension Association support groups will be offered to all participants. You may also contact Catherina Madani or Sandra Lombardi with any research related problems. There is also a risk of subject information being released accidentally. All participant identification will be removed before computer entry or analysis is performed. Study related material will be stored in a locked office on a password protected computer.

Because this is a research study, there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings.

The alternatives to participation in this study are to not complete the surveys offered; the demographic and clinical tool, the MOS-SS and the MSAS. UCSD pulmonary doctors will not be notified of which patients have chosen to participate or not in the study and your care with not be affected if you participate or not.

There may or may not be any direct benefit to you from these procedures. The investigator[s], however, may learn more about ways to better identify patients who may benefit from symptom m management and supportive options such as palliative care.

Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without penalty or loss of benefits to which you are entitled. If you decide that you no longer wish to continue in this study,you will not need to complete any surveys from our investigators. You may also contact Catherina Madani or Sandra Lombardi to let them know that you no longer wish to continue in this study.

#130873

You may be withdrawn from the study for any reason. You may also be withdrawn from the study if you do not follow the instructions given you by the study personnel.

You will be told if any important new information is found during the course of this study that may affect your wanting to continue.

No compensation for your time and travel will be provided.

There will be no cost to you for participating in this study.

If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at (858) 657-5100 for more information about this, to inquire about your rights as a research subject or to report research-related problems.

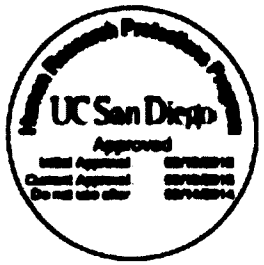
Research records will be kept confidential to the extent allowed by law. The records of subjects names and associated study number will be kept secure in the PI's locked office at UCSD. Research records may be reviewed by the UCSD Institutional Review Board.

Catherina Madani, RN or Sandra Lombardi, RN have explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Catherina Madani at 858-657-6727 or cmadani@ucsd.edu

You have received a copy of this consent document and a copy of the "Experimental Subject's Bill of Rights" to keep.

You agree to participate.

Subject's signature	Witness	Date



APPENDIX B

Demographic Data Sheet

Directions: These questions concern the backgrounds of those who respond to this questionnaire. As with all answers to this survey, your responses will be kept confidential. Please circle the appropriate letter or fill in the blank.

1.What is your gender? (circle one): Female Male

2. What is your age? _____

3. What is your race or ethnicity? (Circle all that apply)

White African-American/Black Hispanic/Latino Asian Other

4. What is your current marital status? (circle one):

Married Divorced Separated Widowed Single-never married

5. Living arrangements (circle one):

Lives alone Lives with family/friends Lives in facility

6. How many years of school have you received? (circle one):

College graduate Some college High school graduate Some high school

7. What is your work status? (circle one):

Fulltime Part-time Retired Student Disabled

8. What is your Insurance Coverage (circle one)

Medicare Medical Commercial/private Other

9. How long ago were you diagnosed? (month /year of diagnosis or time since diagnosis)_____

10. If you are on continuous infusion (SQ or IV) how long have you been on it? (months or date)_____

11. How many doctor's appointments in the past 6 months? (circle one):

0 1 2 3 4 5 <5

10.How many trips to the emergency room in the past 6 months? (circle one):

0 1 2 3 >3

11.What was the reason for the visits?

_____

12.How many hospital admissions in the past 6 months? (circle one):

0 1 2 3 >3

13.What was the reason for the admission?

_____

APPENDIX C

Memorial Symptom Assessment Scale

MEMORIAL SYMPTOM ASSESSMENT SCALE															
Name									Date						
Section 1															
Instructions: We have listed 24 symptoms below. Read each one carefully. If you have had the symptom during this past week, let us know how OFTEN you had it, how SEVERE it was usually and how much it DISTRESSED or BOTHERED you by circling the appropriate number. If you DID NOT HAVE the symptom, make an "X" in the box marked "DID NOT HAVE."															
DURING THE PAST WEEK Did you have any of the following symptoms?	DID NOT HAVE	IF YES How OFTEN did you have it?				IF YES How SEVERE was it usually				IF YES How much did it DISTRESS or BOTHER you?					
		Rarely	Occasionally	Frequently	Almost Constantly	Slight	Moderate	Severe	Very Severe	Not at all	A Little Bit	Somewhat	Quite a Bit	Very Much	
Difficulty concentrating		1	2	3	4	1	2	3	4	0	1	2	3	4	
Pain		1	2	3	4	1	2	3	4	0	1	2	3	4	
Lack of energy		1	2	3	4	1	2	3	4	0	1	2	3	4	
Cough		1	2	3	4	1	2	3	4	0	1	2	3	4	
Feeling nervous		1	2	3	4	1	2	3	4	0	1	2	3	4	
Dry mouth		1	2	3	4	1	2	3	4	0	1	2	3	4	
Nausea		1	2	3	4	1	2	3	4	0	1	2	3	4	
Feeling drowsy		1	2	3	4	1	2	3	4	0	1	2	3	4	
Numbness/tingling in hands/feet		1	2	3	4	1	2	3	4	0	1	2	3	4	
Difficulty sleeping		1	2	3	4	1	2	3	4	0	1	2	3	4	
Feeling bloated		1	2	3	4	1	2	3	4	0	1	2	3	4	
Problems with urination		1	2	3	4	1	2	3	4	0	1	2	3	4	
Vomiting		1	2	3	4	1	2	3	4	0	1	2	3	4	
Shortness of breath		1	2	3	4	1	2	3	4	0	1	2	3	4	
Diarrhea		1	2	3	4	1	2	3	4	0	1	2	3	4	
Feeling sad		1	2	3	4	1	2	3	4	0	1	2	3	4	
Sweats		1	2	3	4	1	2	3	4	0	1	2	3	4	
Worrying		1	2	3	4	1	2	3	4	0	1	2	3	4	
Problems with sexual interest or activity		1	2	3	4	1	2	3	4	0	1	2	3	4	
Itching		1	2	3	4	1	2	3	4	0	1	2	3	4	
Lack of appetite		1	2	3	4	1	2	3	4	0	1	2	3	4	
Dizziness		1	2	3	4	1	2	3	4	0	1	2	3	4	
Difficulty swallowing		1	2	3	4	1	2	3	4	0	1	2	3	4	
Feeling irritable		1	2	3	4	1	2	3	4	0	1	2	3	4	

Section 2										
INSTRUCTIONS: We have listed 8 symptoms below. Read each one carefully. If you have had the symptom during this past week, let us know how SEVERE it was usually and how much it DISTRESSED or BOTHERED you by circling the appropriate number. If you DID NOT HAVE the symptom, make an "X" in the box marked "DID NOT HAVE."										
DURING THE PAST WEEK. Did you have any of the following symptoms?	DID NOT HAVE	IF YES How SEVERE was it usually?				IF YES How much did it DISTRESS or BOTHER you?				
		Slight	Moderate	Severe	Very Severe	Not at all	A little bit	Somewhat	Quite a bit	Very much
Mouth sores		1	2	3	4	0	1	2	3	4
Change in the way food tastes		1	2	3	4	0	1	2	3	4
Weight loss		1	2	3	4	0	1	2	3	4
Hair loss		1	2	3	4	0	1	2	3	4
Constipation		1	2	3	4	0	1	2	3	4
Swelling of arms or legs		1	2	3	4	0	1	2	3	4
"I don't look like myself"		1	2	3	4	0	1	2	3	4
Changes in skin		1	2	3	4	0	1	2	3	4
IF YOU HAD ANY OTHER SYMPTOMS DURING THE PAST WEEK, PLEASE LIST BELOW AND INDICATE HOW MUCH THE SYMPTOM HAS DISTRESSED OR BOTHERED YOU.										
Other:						0	1	2	3	4
Other:						0	1	2	3	4
Other:						0	1	2	3	4

APPENDIX D

Chart Audit Tool

Chart Audit Measure (To be done by the PI)

1. RAP_____ Date of heart catheterization_____
2. CO_____
3. CI _____
4. PVR _____
5. Six minute walk test _____Date_____
6. Comorbidities_____
7. Functional Status_____
8. PAH Type_____
9. PAH medications _____

_____

Health care Utilization Pattern Chart review

1. Number of hospitalization in the past 6 months_____
2. Reason for admission_____
    a. **Hospital LOS**_____
3. Number of ED visits in the past 6 months_____
4. Reason for ED
5. Number of clinic visits in past 6 months_____

APPENDIX F

University of San Diego Institutional Review Board Approval Letter

130873

UNIVERSITY OF CALIFORNIA, SAN DIEGO
HUMAN RESEARCH PROTECTIONS PROGRAM

TO: Dr. Michael Madani

RE: Project #130873
Predictors of Symptom Burden in Pulmonary Arterial Hypertension

Dear Dr. Madani:

The above-referenced project was reviewed and approved by one of this institution's Institutional Review Boards in accordance with the requirements of the Code of Federal Regulations on the Protection of Human Subjects (45 CFR 46 and 21 CFR 50 and 56), including its relevant Subparts. This approval, based on the degree of risk, is for 365 days from the date of IRB review and approval unless otherwise stated in this letter. The regulations require that continuing review be conducted on or before the 1-year anniversary date of the IRB approval, even though the research activity may not begin until some time after the IRB has given approval.

The Committee notes that this study is closed to accrual; re-approved consent forms will not be provided to the PI.

The IRB determined that this project presents no more than minimal risk to human subjects in that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Date of IRB review and approval: 7/17/2014

On behalf of the UCSD Institutional Review Boards,

/rc
Kevin "Casey" Cox
Acting Director
UCSD Human Research Protections Program
(858) 657-5100; hrpp@ucsd.edu

Note: IRB approval does not constitute funding or other institutional required approvals. Should your studies involve other review committees such as Office of Clinical Trials Administration (OCTA), Office of Coverage Analysis Administration (OCAA), Conflict of Interest (COI), Protocol Review Monitoring Committee (PRMC), and committees under Environmental Health & Safety (EH&S) such as Institutional Biosafety Committee (IBC), Human Exposure Committee (HERC), and RSSC (Radiation Safety and

Surveillance Committee), it is the researchers responsibility to ensure that all approvals are in place prior to conducting research involving human subjects or their related specimens.

Approval release date: 7/24/2014

APPENDIX G

University of San Diego Institutional Review Board Approved Recruiting Script

Project # 130873 Predictor of Symptom Burden in Pulmonary Arterial Hypertension

Requested Brief Recruiting Script

Hello My name is…(Catherina Madani or Sandra Lombardi) a nurse here at UCSD.

I am here today to tell you about a study that I am conducting with Michael Madani. We want to understand what it is like to live with pulmonary arterial hypertension, in particular, what it is like to live with the symptoms associated with the disease. With a better understanding of what it is like to live with the disease and specific medical markers (for example pulmonary pressures and right heart function), we are hoping to be able to identify people who might benefit from additional supportive care in combination with their present medical care earlier in the disease process, such as palliative care. This study's goal is to better understand what it is like to live with pulmonary arterial hypertension and help identify people who may need extra supportive services.

If you are interested in participating I have some paper work that I would need you to fill out starting with the consent, which I will be happy to go through with you….