

Depression in pulmonary arterial hypertension: An undertreated comorbidity

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a debilitating condition leading to progressive decline in functional capacity. As a result, PAH can lead to psychological impairment that can impact the overall disease status. The medical community has developed several screening questionnaires in order to assess depression in their patients allowing physicians to be at the forefront of recognizing clinical depression. There is a suggestion that depression symptomatology is more prevalent in the PAH population. The aim of this article is to review the current thought process about diagnosis and management of depression in PAH patients.

KEY WORDS: Depression, psychotherapy, pulmonary arterial hypertension, pulmonary rehabilitation screening questionnaire

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a debilitating lung disease characterized by persistent elevation of pressure in the pulmonary arteries and pulmonary vascular resistance leading to right heart failure resulting in a progressive decline in the level of functioning.^[1] Patients present with increased shortness of breath on exertion, palpitations, and fatigue, making it difficult to differentiate these symptoms from other cardiopulmonary diseases. Medical research in the past three decades has changed management approach to this disease and today medical therapies such as prostanoids, phosphodiesterase type-5 inhibitors (PDE-5) and endothelin receptor antagonists (ERAs) are available to improve exercise tolerance.^[2] These medications have reduced mortality and improved exercise capacity and pulmonary hemodynamic parameters.^[2] Despite these innovations, it is recognized that the debilitating natural history of PAH provides a significant challenge for patients and physicians.^[3] PAH patients suffer from many comorbidities. Depression remains one such

prominent comorbidity. The aim of this article is to review the current literature of depression in PAH.

RESEARCH IN PULMONARY ARTERIAL HYPERTENSION AND DEPRESSION

Depression is a serious illness characterized by an intense feeling of sadness associated with emotional and behavioral changes affecting anyone regardless of age, race, gender, or socioeconomic status. Patients can feel (a) hopelessness (b) helplessness (c) worthlessness (d) agitated (e) fatigue (f) lack of interest (g) decreased concentration (h) suicidal thoughts, and (i) appetite changes.^[4] A clinical diagnosis of depression requires patients to have five or more of the nine symptoms in a 2-week period.^[4] These symptoms have a significant effect on the patient's level of functioning and as a result, interfere with daily activities.^[4] Depression may be difficult to detect because of lack of specific laboratory parameters pointing toward it. In clinical practice, depression can also

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Table 1: Major studies of PAH and depression

Trial/Year	Study design	N	Screening instruments	Results
Shafazand <i>et al.</i> /2004 ^[10]	Cross-sectional	53 PAH [†]	(NHP) [†] Congestive heart failure questionnaire (CHFQ) ^{††} Hospital anxiety and depression Scale (HADS) ^{†††}	Moderate to severe anxiety (20.5%) and depression (7.5%) 29% accept risk of death Moderate to severe impairment in NHP domain Moderate to severe impairment in HRQoL ^{^^} domains Patients on epoprostenol had more energy, less emotional stress Patients who were given no epoprostenol had more anxiety and depression
Lowe <i>et al.</i> /2004 ^[11]	Cross-sectional	164 PH [±] 164 IRDs ⁼⁼ 164 PC ⁼⁼⁼	PHQ ^{††}	58/164 (35%) of PH patients had MD ^{^^^} Major depression (15.9%) Panic disorder (10.4%) More MD is PH patients compared to IRDs (27.4%) and PC (24.4%) Prevalence of depression/anxiety strongly associated with declining NYHA FC 14/58 (24.1%) received psychiatric meds 45% with work disability
White <i>et al.</i> /2006 ^[13]	Cross-sectional	46 PAH [†]	Cognitive scales BDI [*] BAI ^{**} SF 36 ^{***}	27/46 (58%) had cognitive sequelae 26% moderate to severe depression 19% moderate to severe anxiety Decreased QoL with worse working memory
Looper <i>et al.</i> /2009 ^[12]	n/a	52 PH [±]	BDI [*] SF 36 ^{***}	21% moderate to severe depression Moderate to severe depression with worse physical functioning
McCollister <i>et al.</i> /2010 ^[14]	Observational	100 PAH [†]	PHQ-8 [†]	15% patients had major depression 40% patients had mild to moderate depression 45% patients had no- to- minimal depressive symptoms 23/90 (25%) patients on antidepressant therapy
Harzheim <i>et al.</i> /2013 ^[15]	Prospective	158 patients 138 PAH [†] 20 CTEPH	SF 36 ^{***} PHQ-9 [†] GAD-7 [^]	22.8% patients had moderate to severe anxiety or depression Moderate to severe MD ^{^^^} had lower QoL [†] 8% received psychiatric meds

[†]PAH: Pulmonary arterial hypertension, [±]NHP: Nottingham health profile, ^{††}CHFQ: Congestive heart questionnaire, ^{†††}HADS: Hospital anxiety and depression Scale, ^{^^}HRQoL: Health related quality of life, [±]PH: Pulmonary hypertension, ⁼⁼IRDs: Inflammatory rheumatic diseases, ⁼⁼⁼PC: Primary care, ^{††}PHQ: Patient health questionnaire, ^{^^^}MD: Mental disorder, ^{*}BDI: Beck depression inventory, ^{**}BAI: Beck anxiety inventory, ^{***}SF 36: Short form 36 health survey, [†]PHQ-8: Patient health questionnaire 8, [†]PHQ-9: Patient health questionnaire 9, [^]GAD-7: Generalized anxiety disorder questionnaire 7, [†]QoL: Quality of life

be sometimes difficult to diagnosis because of the overlap of symptoms between depression and medical conditions.^[5] Even when patients meet the criteria of depression, the stigma and misconceptions associated with it can make them skeptic about openly seeking help or having an open discussion with health care providers.

The association between depression and PAH has been established [Table 1]. Once a diagnosis of PAH is confirmed, patients have to cope with mixed emotions of understanding and accepting the reality in conjunction with adjustment to their condition [Figure 1]. The complex nature of PAH, an uncertain future, and a lack of cure can impel feelings of being overwhelmed and the inability to maintain regular social activities.^[6,7] As a result, patients report restrictions in their ability to perform daily tasks such as working, traveling, shopping, and household chores.^[8] A recent international survey of PAH patients found them to have feeling of worthlessness (22%), frustration (35%), anger (24%), and little pleasure in activities (25%) that they enjoyed prior to PAH diagnosis.^[8] As patients struggle to cope with an unfamiliar condition, they are frustrated in keeping up with their doctor’s appointment, magnitude of multiple tests, and expenses associated with PAH management. Additionally, poor sleep quality is common among these patients and it is related to dyspnea, depression, and quality of life (QoL).^[9] This insurmountable burden can serve as a medium for

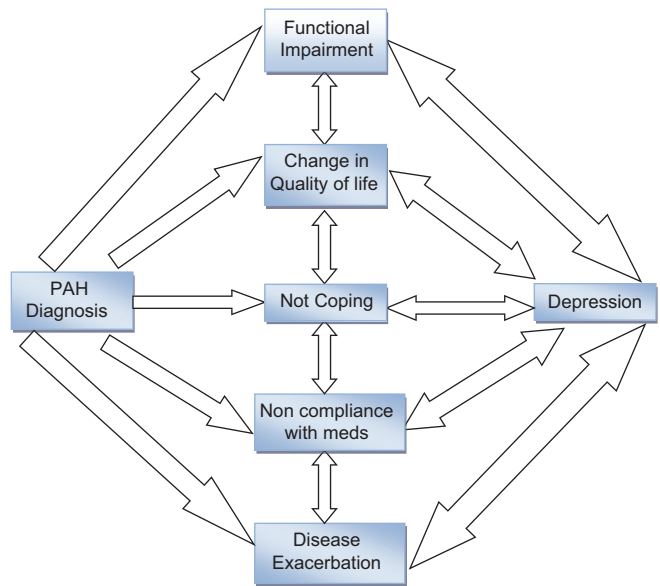


Figure 1: Relationship between pulmonary artery hypertension and depression

self-doubt and noncompliance with medication, which in effect raises health care costs.

Shafazand *et al.* conducted a study that used Nottingham Health Profile (NHP), Congestive Heart Failure Questionnaire (CHQ), with Hospital Anxiety and

Depression Scale (HADS) as a component to assess overall health-related QoL in PAH patients.^[10] A total of 53 patients [mainly New York Heart Association (NYHA) functional class III and IV] were included in the study and were divided into treatment (53% on epoprostenol therapy) and no treatment (47% no epoprostenol therapy) groups. The patient group not on therapy had significantly more anxiety and depression as compared to the medication group. On average, PAH patients reported moderate to severe degree of impairment in all domains of the QoL such as social isolation and emotional reaction. Participants were so unhappy with their lifestyles that (29%) were prepared to take a risk of death in order to be free of the symptoms of PAH.^[10]

Lowé *et al.* investigated the prevalence of anxiety and depression in pulmonary hypertension (PH) patients.^[11] In this study, 164 patients were matched in two comparison groups, inflammatory rheumatic diseases (IRDs) and primary care (PC) patients, who completed a standardized, validated and self-administered patient health questionnaire (PHQ). The study found that patients with PH were diagnosed with one or more mental disorders such as anxiety and depression more commonly compared to IRD and PC patients.^[11] There was also evidence that in PAH patients, as the functional class declined, the frequency of mental disorders increased from (17.7%) in NYHA (Class I) to (61.9%) in NYHA (Class IV). Of the patients, 24.1% received some kind of treatment for their mental disorder.^[11] Thus, there was also a strong association between increasing functional impairment and mental disorders.

Looper *et al.* investigated depressive symptoms and its association with the physical symptoms of PH.^[12] Fifty-two patients, both precapillary and postcapillary PH patients, who were included in this trial completed the Beck Depression Inventory (BDI) questionnaire for depression and it was found that physical functioning was significantly associated with depressive symptoms. Moderate to severe depression significantly worsened physical function scores in comparison to minimal or no depressive symptoms.^[12] White *et al.* evaluated emotional and cognitive impairments in PAH patients. BDI questionnaire was used in 46 patients and it was found that 26% of the patients had some symptoms of moderate to severe depression.^[13]

McCollister *et al.* studied the prevalence of depression in a PAH as a primary endpoint, using PHQ-8.^[14] A total of 100 patients were enrolled in the trial and at two separate outpatient visits, the questionnaires were completed and functional class assessment and 6-min walk distance (6MWD) were performed. A high prevalence of depressive symptoms (55%) was found in this study population but only 25% of the patients were taking any type of antidepressant medication.^[14] This study highlighted that depression treatment was being underutilized in this population.^[14]

Harzheim *et al.* demonstrated that moderate to severe depression was significantly correlated with a lower QoL but not with long-term survival.^[15] This prospective study of 158 patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH) patients used PHQ-9 and Generalized Anxiety Questionnaire-7 (GAD-7) for assessment. Patients with a high GAD-7 value also had a high PHQ-9 value, thus suggesting a significant correlation between the severity of anxiety and depression disorders.^[15] In addition, 57.6% of the patients with moderate to severe mental disorder had significant impairment in their daily activities, as compared to patients with no or mild depression (11.7%). Among the patients, 22.8% presented with moderate to severe anxiety or depression and out of them, only 8% were receiving any psychopharmacological treatment.^[15] A recent cross-sectional survey was performed to examine the correlation of depression, anxiety, and its effects on 6MWD and health-related quality of life (HRQoL) in PH patients.^[16] Tartavouille *et al.* conducted a survey of 166 patients by completing Depression Anxiety Stress Scale (DASS) and the Dartmouth Cooperative Functional Assessment Charts. The findings of this survey were indicative of a link between stress anxiety and QoL with PH.^[16]

SCREENING FOR DEPRESSION

Screening for depression in the PAH population remains challenging because depressive symptoms such as low energy or fatigue can be viewed as part of the underlying disease process. Therefore, they can sometimes be ignored. A lack of proper training skills in treating physicians may also play a role in not detecting underlying depression.^[7]

Recently, the US Preventive Services Task Force has recommended health care providers to screen and provide effective treatment for depression in adult patients.^[17] One method of screening for depression is to utilize questionnaires that have been developed over the years. These questionnaires have been validated by research and extensively used in many chronic conditions.^[18] Some of the screening tools available are Zung Self-rating Depression Scale, Center for Epidemiologic Studies-Depression Scale (CES-D), PHQ-9, and BDI.^[18] These scales are simple to complete and can be done while patients are waiting in doctors' offices to be seen by a physician. Patients suspected of depression, based on the screening questionnaires, should therefore, undergo a thorough assessment to determine the presence or severity of depression. As patients are being assessed for depression, risk of suicide should be assessed very meticulously by their physicians.

MANAGEMENT OF DEPRESSION IN PULMONARY ARTERIAL HYPERTENSION

Depression is a treatable condition. However, the exact pharmacotherapy for treatment for a PAH patient needs to be well-defined. There is limited and contentious data

on the use of certain antidepressants such as selective serotonin reuptake inhibitors (SSRIs) for PAH patients. Kawut *et al.* performed a retrospective study of 84 patients, out of which 13 patients were taking SSRIs. The study observed that PAH patients had a lower risk of death (50%) compared to those not treated with SSRI.^[19] These findings were inconsistent with other reports. Sadoughi *et al.* explored the relationship between SSRI use and PAH. PAH patients taking SSRI were at high risk of mortality and clinical worsening than patients not taking SSRIs.^[20] Huybrechts *et al.* examined the association between high morbid pregnancy and antidepressant medication usage leading to the development of persistent pulmonary hypertension of the newborn (PPHN).^[21] The finding of this large cohort suggests that SSRI exposure in late pregnancy is associated with increased risk of PPHN; however, the risk was found to be smaller than what was previously proposed.^[21]

The best treatment for depression in PAH patients is not known. PAH patients are already on multiple medications and it conceivably raises the possibility of assessing a nonpharmacological outlook for the treatment of depression. As part of an integrative approach to depression, guidelines are available to efficiently treat it with medication and psychotherapy. Current guidelines for depression in the general population recommend the usage of a combination of medication and psychotherapy for moderate to severe depression while psychotherapy along with this can be a valuable first step for mild depression.^[22] However, whether this applies for PAH patients or not has not been studied. Psychotherapy is an effective form of treatment for depression that allows patients to converse with a health care professional. It is a method that helps patients to understand their behavior that might have contributed to depression. One particular form of psychotherapy is cognitive behavioral therapy (CBT). The basic principal of CBT is a focused, structured collaborative environment to assist patients in solving problems and dysfunctional thinking.^[13] It is a collaborative effort between patients and clinicians to apply valuable strategies that can help patients to gain control.^[13] Such strategies have been used in chronic obstructive pulmonary disease (COPD) patients.^[23] However, there is a paucity of data regarding CBT in the PAH cohort.

In addition to behavioral therapy, support groups can also be considered as part of a new innovative option for patients. Support groups are voluntary gatherings of patients and their family members that allow them to share their personal experiences with other patients.^[24] It is an opportunity to simultaneously provide and receive support, build acquaintances, and share coping strategies. A well-functioning support system can empower patients to manage their condition more wholeheartedly. Support groups can have a positive impact on the motivation, confidence, and general well-being of the patient.^[25]

Flattery *et al.* illustrated that patients actively seek support groups as a way of learning about the disease and methods to cope with the uncertainty associated with it.^[26]

More recently, pulmonary rehabilitation (PR) has emerged as an important and integral part of clinical management of chronic respiratory diseases. There is evidence that PR improves function, disease symptoms, fatigue, and QoL in COPD and CHF patients.^[27] PR has been commonly used as a part of standard of care in COPD and CHF patients.^[28,29] Our own data support the perception of improvement in fatigue in advance lung disease after the completion of a PR program. Talwar *et al.* found in a cohort of 21 patients a significant improvement in fatigue and suggested an improvement in depression symptoms after completing PR.^[30] There is an increasing thought process that pulmonary exercise may be beneficial in these patients and clinical data are suggestive of the usage of PR in improving depression. Mereles *et al.* evaluated the effects of daily exercise in a 15-week trial of 36 patients.^[31] At the end of 15 weeks of PR, there was a mean improvement of 111 m in the 6MWD. Exercise training was associated with significant improvement in the QoL as measured by SF-36 questionnaire.^[31] The effects of PR on inspiratory muscle training have also been recently investigated. Saglam *et al.* recruited 29 stable PAH patients who were either in a inspiratory muscle training (IMT) group or a control group for 6 weeks and their QoL was assessed by Nottingham Health Profile (NHP). After completion of PR, patients in the IMT group had considerable improvement in muscle strength as well as emotional and psychosocial dynamics.^[32] Another contemporary approach as an adjunctive therapy for anxiety and depression is progressive muscle relaxation (PMR) techniques, PMR is technique developed to relax various body muscles in order to manage anxiety and stress.^[33] Li *et al.* recruited 130 PAH patients who were randomized to be either the control group or treatment group for 12 weeks.^[34] In comparison to the controls, the study found that patients in the treatment arm had significant improvement in depression and overall QoL.

MOVING FORWARD

Managing important comorbidities is an important aspect of treating any disease with poor outcome. A similar conclusion can be made in the case of PAH. This coexistence of PAH and depression presents health care workers with a challenge but also an opportunity. It is a challenge because of lack of appropriate guidelines for confronting depression with PAH and therefore, leaving its treatment to the clinical judgment of physicians and patient preference. Limited studies have highlighted its significance; the exact association has not been fully addressed. Unfortunately, large scale clinical trials at times may not be possible because of competing illnesses, limited resources, and infrastructure.^[35] In such cases, conducting observational studies is beneficial in identifying PAH patients with depression.^[35]

It is also the right opportunity for health professionals to focus on a) obstacles in diagnosing depression, b) addressing obstacles in treating depression, and c) clarifying the ideology of using depression as an outcome measure and its relationship to 6MWD, if any. With this approach, perhaps health care policy-makers can also create methodical guidelines in approaching depression and helping physicians in avoiding a medical conundrum of whether or not to use medications.

Finally, to address the fundamental shortcomings of health care delivery, an efficient and effective chronic care model should be created for PAH patients, as similar models have shown evidence of improved care for congestive heart failure,^[36] diabetes mellitus,^[37] and asthma.^[38] Six keys elements have been identified in the chronic care model: Health system redesign, decision support, information systems, community involvement, organization, and self-management support for empowering patients [Table 2].^[39] By developing a chronic care model for PAH patients, it will propel physicians toward the establishment of a patient-centered outcome approach. This “patient-centered” outcome approach can empower physicians to embrace web portal-like electronic medical records (EMRs) by allowing effective, efficient, and accurate communication with other team members in patient care. Simple tools embedded in EMRs such as medication dosing or side-effect profile can be helpful in decision-making. Moreover, health portal websites have enabled patients to be more informative about their condition and empower them as well to share responsibility in the management. These simple measures can ensure that patients get optimal care and hence, bring an overall improvement in the treatment outcome.

SUMMARY

PAH patients have multiple comorbidities. Depression is an important comorbidity that increases the overall

Table 2: Components of chronic care model (adapted from Wagner *et al.* 2001)^[39]

Delivery system design
Interdisciplinary care teams delivering effective and efficient care
Innovative patient interactions
Improved health promotion and prevention
Decision support
Physicians use evidence-based guidelines as standard of care
Physicians have access to specialist for collaboration
Information systems
Create registries for specific diseases
Monitor patient health status
Internet based portals
Involving community
Community based interventions
Organization
Have dedicated strong leaders
Improve quality of care
Empowerment
Support and empower patient's to manage care
Engage patient's in decision making
Encourage support group interactions

burden of PAH. Accordingly, it is possible to detect depression early by using screening questionnaires and treat it without delay. This may help in reducing distress, improving daily functioning, and leaning toward living a better QoL. While there is a paucity of data about the psychopharmacological agents for PAH patients, we believe that psychological support and PR are an important adjunctive therapy. For that reason, more qualitative research is needed to precisely define their roles in PAH management.

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Conflicts of interest

There are no conflicts of interest.

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