

Adherence to Medication in Patients with Pulmonary Arterial Hypertension

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Received: January 10, 2018; **Published:** February 20, 2018

Abstract

Pulmonary arterial hypertension (PAH) is a progressive condition characterized by increased pulmonary vascular resistance and increased pulmonary arterial pressure leading to right ventricular failure and death [1]. At present there is no cure for PAH, however, cutting edge medical research over the past few decades continues to improve our knowledge about the pathological process. This has led to development of medication that can slow disease progression and improve functional capacity. There is evidence that suggests that medications have improved quality of life and increased survival, yet due to the chronic nature of PAH and multiple doses of medications; adherence to medication is an important issue.

Keywords: Chronic Disease; Pulmonary Arterial Hypertension; Screening Questionnaire; Non-Adherence; Medication

Introduction

Medication adherence is an important and complex aspect of any chronic disease. Adherence is defined as an active process that reflects a patient's ability to follow medical instructions as part of an agreement with their physicians [2]. In contrast, compliance is simply defined as a passive process of patient ability to take the prescribed medication [3]. Both adherence and compliance are often used interchangeably; the latter term is generally viewed with a negative connotation for its paternalistic attitude between physician and their patients [4]. For this reason, over the years adherence has become a more acceptable alternative to compliance.

Adherence

Adherence has been studied in many diseases such as tuberculosis, hypertension and breast cancer [5,6]. It is estimated that 50% of patients with chronic disease don't take medications as prescribed [2,3]. Consequently, this can lead to a suboptimal response, disease exacerbation, and increased utilization of the healthcare system with more frequent visits to the emergency room and/or inpatient admission as well as increase morbidity and mortality [7,8]. Study by Ho., et al. found that non-adherence to cardio-protective medications (Beta blockers, ACE inhibitors and statins) increased the risk of cardiovascular mortality by 28.8%, 21.6% and 26%, respectively [7].

The reasons for non-adherence are relatively complex. It is a contribution of various factors including physicians and patients, supplemented by socioeconomic factors (Figure 1). For many patients, a lack of understanding of the disease course and their lack of participation in treatment planning profoundly contributes to non-adherence. Other factors associated include, fear of side effects profile, excessive costs and complex regimens [9,10]. Health literacy for the patient is also a key component for maintaining medical adherence [11,12]. Roumie., et al. conducted a study of one thousand three hundred and forty one patients with hypertension and patient educa-

tion [13]. This prospective study concluded that education of both physician and patient was associated with improved blood pressure control than education of physician alone [13]. Aside from patient factors, clinical factors are an important determinant of adherence. A lack of constructive communication, a weak doctor-patient relationship and unavailability of healthcare providers to explain the disease process and treatment plans have made it difficult for patients to adhere [3,10]. Other barriers identified for non-adherence are disease factors such as convenience of a pharmacy, duration of treatment, social support, and a complicated dosing schedule [11] (Figure 1). A high copayment for medications is also linked with non-adherence. Cole, *et al.* conducted a retrospective cohort study to measure association of copayment with medication adherence in heart failure patients. The study found that, an increase in medication copayment of \$10 resulted in the adherence dropping to 2.6% and there was a 6.1% increased risk of hospitalization for Congestive Heart Failure [14]. Another reason for non-adherence is patient’s inability to remember taking medication.

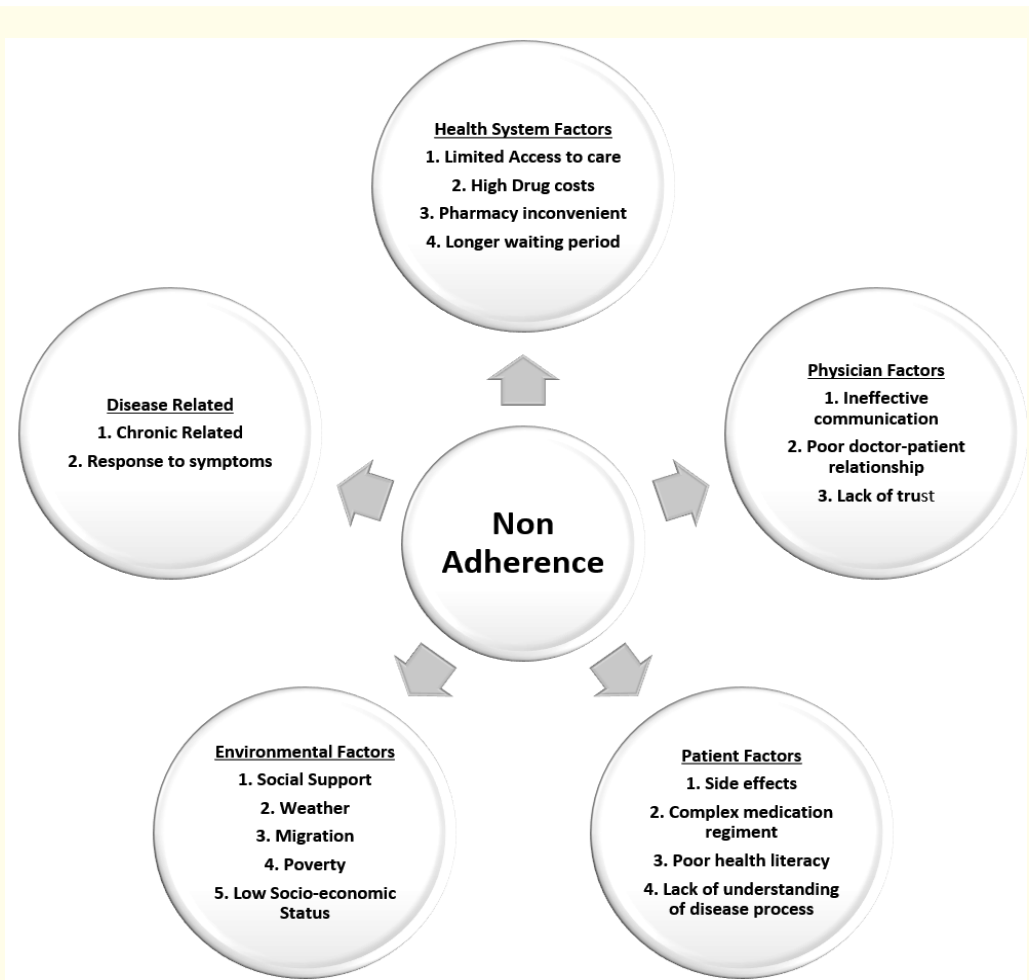


Figure 1

Medication adherence in PAH

Although a cure remains elusive, the pathophysiological understanding of PAH has led to development of medications that can be divided into four categories: Phosphodiesterase type 5 inhibitors (PDE-5), Soluble guanylate cyclase (sGC), Endothelin receptor antagonists (ERAs) and Prostacyclin analogues. Similar to other chronic diseases, adherence to PAH medications remains a challenge. Currently, very little is known about the extent and impact of non-adherence as well as barriers to PAH medications.

Medication Class	Medication name	Dose form	Common reason for non-adherence
Endothelin receptor antagonists	Ambrisentan Bosentan Macitentan	All Oral forms	Liver function tests for Bosentan
Phosphodiesterase type 5 inhibitors	Sildenafil Tadalafil	All Oral forms	Frequent dosing for Sildenafil
Prostacyclin analogues	Epoprostenol Treprostinil Iloprost	Intravenous Infusion/Inhalation/Oral Inhalation	Frequent dosing, complicated delivery system, social awkwardness
Soluble guanylate cyclase stimulator	Riociguat	All Oral forms	--
Prostacyclin receptor agonist	Selexipag	All Oral forms	--

Table 1: PAH Medications.

These medications can be delivered orally, parentally or by way of an inhaled route. Oral route provides a more convenient way due to its simplicity. However, oral therapy may pose some challenges with regards to adherence due to the frequency of dosing and monitoring. Waxman, *et al.* assessed factors associated with adherence to PDE-5s in PAH population. In a study of two thousand one hundred and forty three patients, 60.7% patients remained adherent to a daily dose of tadalafil; compared to 44.3% patients adhered to sildenafil that is taken three times/day [15]. One specific ERA, in particular, Bosentan requires routine lab testing for liver functions tests (LFTs), thus patients may be reluctant for more frequent testing [16]. Beside frequency, oral PAH therapy can be financial burdensome with high co-pays and various insurance setbacks for the patients [16].

In comparison to oral therapy, inhaled therapy with prostinoids tends to be more challenging as they have multiple dosage requirements along with a challenging and complicated drug delivery system. The drug devices have a complicated and meticulous process of setting up, taking treatment and then cleaning up afterwards. This can interfere with patients active lifestyles [16]. Patients are frequently unwilling to use inhaled therapy due to fear of embarrassment and attracting unwanted attention [16].

Similar to inhaled therapy, patients on infusion therapy may be reluctant to take this medication due to superfluous social awkwardness. Patients may feel embarrassed because it may prompt inquisitiveness amongst strangers about the status of oneself. Medications such as epoprostenol require daily mixing and need to be kept in cold packs to avoid degradation and can be cumbersome for many patients. Moreover, infusion therapy requires special hands on training to deliver medication safely. Infusion therapy also requires adherence to nonspecific techniques to prevent catheter induced infection. In addition, delivery of medication requires a permanent intravenous catheter which can get infected and precipitate hemodynamic collapse. These factors can account for patient's reluctance towards accepting intravenous (IV) therapy as treatment in the first place.

Other ancillary medications, such as diuretics, warfarin and oxygen therapy are effective in managing PAH, if patients adhere to them. However, many patients feel that these medications adversely disrupt lifestyle and quality of life. As a result, patients may lean towards taking medications only for a short period or on an intermittent basis. At times, based on their own assessment of clinical improvement, they may stop completely or taper themselves without a clinician's advice.

Measures of Medication Adherence

With the growing concerns about adherence, it is important to assess the degree of adherence to medications. While there is no gold standard to effectively assess adherence, direct (drug level) and indirect methods (patient diaries) are some of the strategies that can be utilized by physicians (Table 2) [17,18]. A multitude of validated questionnaires have also been developed that provide information for patient's non-adherence [19]. These questionnaires may be less reliable, for PAH patients, however they are easy to use and provide a concurrent feedback for physician's to make clinical judgment (Table 3). Physicians need to consider including these in their day to day practice to promote medical adherence in PAH patients.

Direct	Indirect
Direct observation of ingesting	Prescription refill
Drug Blood levels	Pill counting
Measuring blood biomarkers	Clinical Response assessment
	Electronic monitors
	Patient diaries
	Self-reported questionnaires

Table 2: Methods to access Adherence

Scale/Author/Year	Num. of items	Response options	Score
*MAQ/Morisky, <i>et al.</i> /1986	4	YES (0), NO (1)	0 (High Adherence) 1 - 2 (Medium Adherence) 3 - 4 (Low Adherence)
*MAQ-8/Morisky, <i>et al.</i> /2008	8	Items 1-7 (Yes/No) Item 8 –Likert Scale A- Never/Rarely B- Once in a while C- Sometimes D- Usually E- All the time (A=0, B-E =1)	8 (High Adherence) 6 - 7 (Moderate Adherence) < 6 (Low Adherence)
^BMQ/Svarstad, <i>et al.</i> /1999	9	Regimen Screen (5 items) 0-7 Belief Screen (2 items) 0-2 Recall Screen (2 items) 0-2	Higher score indicate non-adherence
†SEAMS/Risser, <i>et al.</i> /2007	13 Self Confidence (6 items) Complexity of Medication (4 items) Daily life changes (3 items)	1= Non confident 2= Somewhat confident 3= Very confident	13-39, higher score indicate adherence
‡ASK-12/MATZA, <i>et al.</i> /2009	12 3 Domains: 1) Inconvenience/forgetfulness (3 items) 2) Health Beliefs (4 items) 3) Behavior (5 items)	5 point Likert scale	12-60, higher score indicate adherence

Table 3: PAH Medications.

*MAQ-4: Medication adherence questionnaire; *MAQ-8: Morisky Medication Adherence Scale – 8; ^BMQ: Brief Medication Questionnaire; †SEAMS: Self-efficacy for Appropriate Medication Use Scale (SEAMS); ‡ASK-12: Adherence starts with Knowledge Survey (ASK -12)

Medication Adherence Questionnaire

Medication Adherence Questionnaire (MAQ) also referred as Morisky medication adherence questionnaire (MMAS-4), is the shortest and most widely used questionnaire that can identify fundamental barriers to adherence. It has been validated in various conditions and treatments. The 4 questions assess: forgetting, carelessness, stopping the drug when feeling better or starting the drug when feeling worse and is rated with Yes (0) or No (1) and the item scores are then tallied [20].

Morisky Medication Adherence Scale - 8

The Morisky Medication Adherence Scale (MMAS -8) has 8 questions with the first 7 questions in a (yes) or (no) response format. The last item has a 5 point likert scale. Additional items were added with the intention of capturing patient behavior as it relates to non-adherence due to skipping medication deliberately or simply being forgetful. The total score of it is summed up with a range from (0 - 8). A score of 8 reflects high adherence, 7 - 6 reflects moderate adherence and (< 6) reflects low adherence [21].

Brief Medication Questionnaire

Brief Medication Questionnaire (BMQ) is intended to look at patient behavior and barriers to adherence [22]. It consists of 3 screens: Regimen screen (5 items), belief screen (2 items) and recall screen (2 items). The regimen screen measures self-reported adherence behavior over a one week period. If patient indicates non-adherence, they get a score of (1) and score of (0) indicates adherence to medication. The scores range from 0 to 7. The second part (belief screen) looks at patient's view of efficacy of medication, with a concern over short and long term effects. The scores range from 0 to 2. The recall screen assesses patient's ability to recall dosing regimen of medication. In recall, the score ranges from 0 to 2. The overall score of all these screens is 11 with higher score indicating non-adherence.

Self-efficacy for Appropriate Medication Use Scale (SEAMS)

The Self-efficacy for Appropriate Medication Use Scale (SEAMS) contains 13 items, using a 3 point likert scale, and focuses on patients' views on their medication [23]. The 13 questions are divided into 3 sections: self-confidence (6 items) complexity of medication (4 items), daily life changes (3 items). The scale can be used in patients with various literacy skills and cover a variety of chronic diseases. The responses are recorded as non-compliant (1), somewhat confident (2) and very confident (3) Scores range from 13 to 39 with a higher score indicating higher level of self efficacy for medication adhere. Patients are asked questions about their level of self confidence in taking medications accurately in various circumstances [23].

Adherence starts with Knowledge Survey (ASK -12)

The Adherence starts with Knowledge Survey (ASK-12) is a 12 item questionnaire developed to identify factors that influences adherence [24]. The questionnaire is an abbreviated version of ASK 20 that has been validated in the past. In the condensed version, the 12 questions address 3 domains: Inconvenience/forgetfulness (3 items), health beliefs (4 items) and behavior (5 items). Each of the questions is scored in a likert scale ranging from 1 to 5 and scores are tallied with a range of 12 to 60. A higher score represents greater barrier to adherence [24]. This is a generic instrument for diverse ailments.

Future Impact

As the patients disease condition improves, there is always a question of medication adherence. Nevertheless it is an important endeavor to understand various factors associated with medication adherence. The predicament of poor adherence has largely been overlooked by healthcare policy makers. As the healthcare costs skyrocket, effective healthcare policies should be established to address this urgency of non-adherence. In the interim, the majority of the responsibility rests upon physicians and other healthcare providers. For example, a poor response to treatment should raise questions about adherence to medication [17]. One of the most crucial points for physicians is to engage in an effective communication about adherence in an open, empathic, non-judgmental way. Physicians need to play an active role in understanding the motivational and behavioral factors that drive patients towards non-adherence [10]. This allows physicians to form a patient centered activity that directly involves them in making decisions about their health. Patients often come to their doctor's office with either a medication list or medication bag, leaving doctors to assume that their patients are taking all the medications. It is their obligation to ask questions about all the medications [3].

Many factors dictate patients' adherence and each patient is unique, therefore patients need to participate in an adherence evaluation. One way to improve adherence is for the physicians is to ensure that patients understand the information provided to them by using the 'teachback approach' [3]. The 'teach-back approach' is a process in which patients can reiterate what they understood about their medications [3].

The issue of non-adherence also presents a perfect opportunity for health information technology to develop tools to improve adherence. Electronic medical records (EMRs) are becoming universally available and can identify "at risk" non-adherence patients, thus enabling physicians to follow up with these patients more aggressively.

To motivate patients toward medication adherence, patients must be educated about their medical condition so that they can play an effective role in management of their own health, which in turn, will empower them to ask questions about their medication. Simplifying a medication regimen to once daily dosing can result in a greater degree of compliance. Claxton, *et al.* conducted a meta-analysis of seventy six studies to observe association between dose regimen and compliance [25]. The study found that compliance a single dose was 79% \pm 14%, at two doses 69% \pm 15%, at three doses 65% \pm 16% and at 4 doses compliance was 51% \pm 20%. The study concluded that as the number of doses increased, the compliance of drug declined [25].

One can utilize physician extenders to educate and explain the importance of medication adherence. Nurses, nurse practitioners and physician assistants are often the patient's first health professional encounter; therefore, they have the responsibility to communicate with patients about medication and reconciling of all medications. They, generally, have a strong relationship with their patients and are in an excellent position to have a non-judgmental conversation about adherence. They can provide supportive links and educational materials for medications. Furthermore, they can conduct follow up telephone calls that can be an effective strategy to reinforce goals of adherence while engaging patients in their treatment plan. Similar to nurses, pharmacists are at an ideal position to directly have an impact on adherence. They are considered a trustworthy source of information and can discuss benefits of adherence. They can reinforce the physicians concern about their health status and medications.

This past decade has seen an exponential growth in internet, e-commerce and its ability to change economic culture. Therefore, there is a great expectation that healthcare should be as accessible, as shopping or banking etc. For instance, smartphone applications can empower patients, providers and caregivers to monitor medication adherence [26,27]. It is a way to provide healthcare services in automated, modified and cost-efficient manner. Along with smartphone applications, reminders sent via mobile text messaging can be a possible way to improve adherence [28]. Thakkar, *et al.* conducted a meta-analysis of sixteen trials of various chronic diseases (HIV, Diabetes Mellitus and Asthma) and concluded that text messaging could improve medication adherence.

In the face of chronic disease, support groups play a vital function. Support groups are place of empowering each other by sharing and learning from others similar experiences [29]. This peer to peer networking can be an effective way to increase medication adherence, as patients can more candidly discuss their concerns about medications.

Conclusion

Medication adherence is a challenge and a major medical problem. A better understanding of the barriers that affect patient's adherence, through carefully designed studies, will help physicians devise effective interventions. In particular, in case of a complex disease like PAH, it is important for physicians to be aware of the possibility of patient's non-adherence, that can lead to significant morbidity and mortality. As a whole, a multidisciplinary approach is needed to improve outcome, as health care professionals have the ability to empower patients to take their medications as prescribed.

Conflict of Interest

None.

Financial Disclosure

None.

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Volume 7 Issue 3 March 2018

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