

Effects of Face-to-Face Nursing Support on Optimal Adherence to Oral Titratable PAH Therapies

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Background: Therapies currently available to pulmonary arterial hypertension (PAH) patients do not reverse the disease; however, they improve pulmonary hemodynamics, offer symptomatic relief, and lengthen the time to clinical worsening. These therapies do not come without their challenges, which include side effects and compliance with challenging titration regimens. Health care providers, particularly nurses, play a significant role in improving patient medication adherence. In-home nurse visits offer disease state education, set medication expectations, and provide support tools for patients when experiencing adverse events that may lead to therapy discontinuation. The purpose of this study is to determine the impact that in-home, face-to-face nursing visits have on optimal adherence to oral PAH therapies.

Methods: We identified patients who received an oral PAH drug (riociguat, selexipag, or treprostinil) supported by a nursing program (study group) and patients who received an oral PAH drug (bosentan, ambrisentan, or macitentan) not supported by a nursing program (control group) using CVS Health pharmacy data from January 1, 2018, to June 30, 2019. A logistic regression model examined demographic and medication factors associated with adherence.

Results: From January 2018 to June 2019, we identified 107 patients in the study group and 213 patients in the control group. After 6 months, patients in the study group reported 0.6 more fill counts (5.1 vs 4.5; $P = .002$) and an 11% higher medication possession ratio (MPR) than those in the control group (86.4% vs 75.0%; $P = .001$). After adjusting for patient characteristics, control patients tended to be more likely to drop therapy in the first 6 months after the index fill (hazard ratio = 1.52; $P = .064$). After 6 months, the study group reported higher rates of therapy persistence than the control group (72.0% vs 60.6%; $P < .05$).

Conclusions: Patients receiving oral PAH therapies (riociguat, selexipag, or treprostinil) supported through a visiting nurse program had significantly higher rates of optimal adherence as demonstrated by a statistically significant improvement in the MPR and a higher prescription fill count than a control group. Ultimately, a multidisciplinary approach supporting the patient and providing patient education, proper motivation, and face-to-face nursing may support improved patient outcomes.

BACKGROUND

Pulmonary hypertension (PH) is a progressive disease characterized by elevated pulmonary vascular resistance. Pulmonary arterial hypertension (PAH), defined as a mean pulmonary arterial pressure of

≥ 20 mm Hg at rest, is a subset of PH that results from increased vascular resistance in the pulmonary arteries and may ultimately result in right heart failure.¹⁻⁷ Over the past 25 years, the number and routes of PAH therapies have increased.

Current PAH therapies are available via intravenous, subcutaneous, inhaled, and oral routes.⁶ Five classes of drugs (phosphodiesterase type 5 inhibitors, guanylate cyclase stimulators, endothelin receptor antagonists [ERAs], prostacyclin analogs, and selective prostacyclin receptor agonists) are Food and Drug Administration (FDA) approved for the treatment of PAH. These drugs target three main pathways: the nitric oxide, endothelin-1, and prostacyclin pathways.^{1,6} While these PAH therapies do not reverse the disease, they do improve pulmonary

Key Words—pulmonary arterial hypertension, optimal adherence, nursing, prostacyclin, endothelin, nitric oxide

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hemodynamics, offer symptomatic relief, and lengthen the time to clinical worsening.⁸ These therapies do not come without their challenges, which include side effects and adherence to challenging titration regimens.

Treatment failure for a patient may result from nonadherence to therapy.⁹ The reasons for nonadherence are complex and may include several factors (age, gender, drug cost, disease severity, comorbidities, medication dosing frequency, side effects, lack of social support, and confusion between the patient and provider when communicating administration instructions).^{10,11} For some patients, a lack of understanding of the disease contributes to nonadherence; thus, patient health literacy is essential to maintaining adherence.¹¹ For other patients, a lack of education, expectations around potential side effects, as well as the time to symptomatic improvement may also contribute to nonadherence. In a prospective study of systemic hypertensive patients, adding patient education to provider education was associated with improved blood pressure control compared to provider education alone.¹²

Health care providers, particularly pharmacists and nurses, play a significant role in improving patient medication adherence; they promote patient care by interacting with both the patient and the provider. Additionally, they are available to assist with patient counseling, disease state education, side effect management, and coordination of care.¹³

While evidence supports the use of an integrated nurse model for the management of specialty diseases,^{14,15} few studies have assessed medication adherence rates among patients with PAH.¹⁶ We hypothesize that in-home, face-to-face nursing visits provide additional patient support around education and side effect management, which leads to improved optimal adherence. The purpose of this study is to determine the impact that nursing visits have on optimal adherence to oral PAH therapies.

METHODS

We conducted a retrospective cohort study of patients with PAH throughout the United States who received

one of six oral PAH drugs (treprostinil [Orenitram], selexipag [Uptravi], riociguat [Adempas], bosentan [Tracleer], ambrisentan [Letairis], and macitentan [Opsumit]) from January 1, 2018, to June 30, 2019. Specific inclusion criteria were (1) male and female patients greater than 18 years of age; (2) new to an oral PAH drug with at least 1 fill between January 1, 2018, and June 30, 2019, and no oral PAH fills 180 days before the index fill; (3) receiving one of the following drugs: treprostinil, selexipag, riociguat, bosentan, ambrisentan, or macitentan; and (4) continuously eligible for pharmacy benefits for the entire study period. We extracted claims from a large national specialty pharmacy for patients who met the inclusion criteria for 180 days after the index fill. The study was reviewed and approved by the Advarra Institutional Review Board as an exempt study under 45 CFR 46.104(d)(4).

Patients were divided into two groups: the study group consisted of those patients on drugs supported by an in-home, face-to-face nursing program (treprostinil, selexipag, and riociguat), and the control group consisted of patients on drugs not supported by such a nursing program (bosentan, ambrisentan, and macitentan). The nursing program may vary by therapy. At the start of care, the nurse meets the patient in their home for disease state education and therapy overview. The nurse walks through therapy-specific patient education materials, reviewing the titration schedules and how frequently the prescriber has ordered to increase their dose along with educating the patient on how to utilize their pharmacy-provided titration guide. While the nurse is in the patient's home, they are assessing the home environment. The field nurses provide updates back to the prescriber on the current dose and/or blood pressure, patient tolerance of the medication, and side effects experienced, if any. Patients are also trained on having an emergency plan and are provided an emergency contact binder and resources to help with any emergency room visits. Riociguat has an average of around 6 in-home visits, which align with the dose increase frequency (every 2 to 4 weeks)

and run through the end of the titration schedule and one additional follow-up visit at month 12 of therapy. For selexipag and oral treprostinil, there is again an initial visit at the start of therapy. The number of selexipag nursing visits is tied to the dose increase schedule. Patients on oral treprostinil had an average of 5 to 6 nurse visits.

Patient feedback from the individual nursing visits is then shared with the specialty pharmacy PAH team and the PAH provider. The specialty pharmacy team communicates closely with the nurses who support PAH patients, making the experience seamless for the patient as relevant health information is shared among the specialty pharmacy nurses, the PAH provider, and the patient.

The following measures were compared by group:

- Standardized 30-day fill count—defined as the total number of days covered by medication divided by 30
- Medication possession ratio (MPR)—defined as the sum of the days' supply of medication divided by 180 (the number of days in the study period)
- First-fill drop-off rate—the percentage of patients with only 1 fill during the study period
- Therapy persistence—the length of time when the patient has medication on hand. If the patient had a 60-day or longer gap without medication after the previous fill was exhausted in each month, they would be considered dropped, and future fills were not taken into account

Descriptive statistics for continuous variables were expressed in the form of means and standard deviations (SDs). Categorical variables were expressed as percentages and numbers of cases. A logistic regression model was utilized to examine demographic and medication factors associated with adherence. A *P* value of .0445 was considered statistically significant. We performed all statistical analyses using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

Table 1. Demographic Characteristics by Group

Parameter	Study group N = 107	Control group N = 213	P value
Age, years, mean (SD) ^a	65.1 (15.1)	55.1 (21.1)	.0001
Male gender, N (%) ^a	49 (45.8)	57 (26.8)	.0006
Median income in the patient household area, mean (SD)	\$52,061 (\$24,577)	\$52,669 (\$20,285)	.8141
College degrees in the patient household area, mean rate (SD)	15.8% (8.0%)	15.4% (7.4%)	.6120
African American, mean rate (SD)	18.7% (25.6%)	18.5% (24.9%)	.2749
Asian, mean rate (SD)	2.3% (3.4%)	4.3% (9.4%)	.0331

Abbreviation: SD indicates standard deviation.

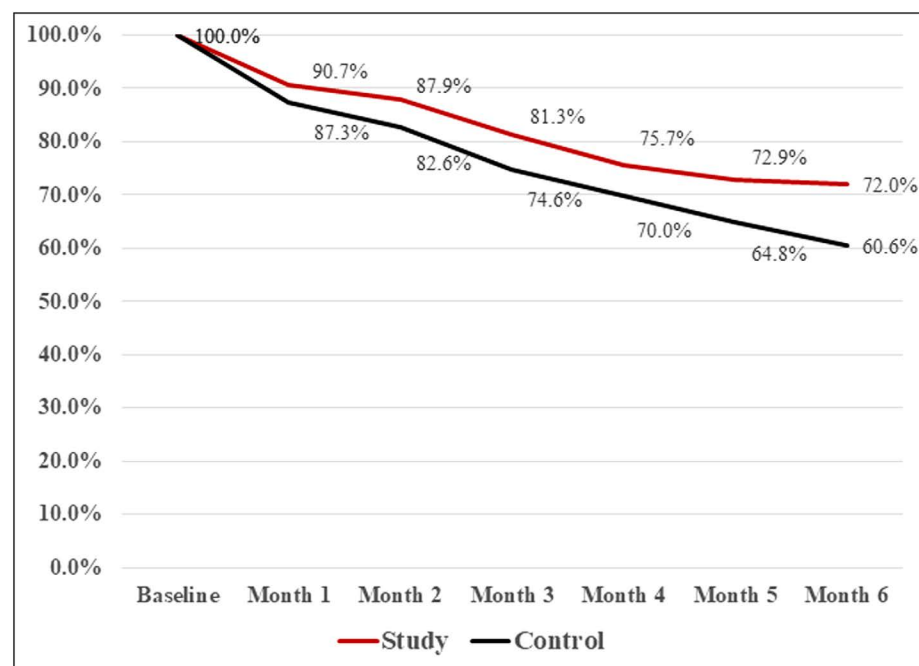
^aThe final statistical model accounted for all differences between patient characteristics.

Table 2. Medication Characteristics by Group

Parameter at 6 months ^a	Study group N = 107	Control group N = 213	P value
Fill count	5.1	4.5	.0016
MPR	86.4%	75.0%	.0013
First-fill drop-off rate	2.7%	5.7%	.1438

Abbreviation: MPR indicates medication possession ratio.

^aControlled for patient characteristics through the regression model.

**Figure 1:** Six-month therapy persistence table by group.

RESULTS

From January 2018 to June 2019, we identified 107 patients in the study group and 213 patients in the control group. The average age of the study group was 65.1 years (SD = 15.1); the

majority of patients were female (54.2%) and white (71%). The average age of the control group was 55.1 years (SD = 21.1); the majority of the patients were female (73.2%) and white (65.7%) (Table 1).

After 6 months, patients in the study group reported 0.6 more fill counts (5.1 vs 4.5; $P = .002$) and an 11.4% higher MPR than those in the control group (86.4% vs 75.0%; $P = .001$) (Table 2).

After adjusting for patient characteristics, control patients tended to be more likely to drop therapy in the first 6 months after the index fill (hazard ratio = 1.52; $P = 0.064$). After 6 months, the study group reported higher rates of therapy persistence than the control group (72.0% vs 60.6%; $P < .05$) (Figure).

DISCUSSION

This study evaluated the impact that in-home, face-to-face nursing visits have on optimal adherence to oral PAH therapies. Overall, patients in the study group achieved higher medication adherence and persistence over 6 months than the control group. Our adherence results are similar to those of Shah et al, who reported high adherence rates among patients receiving care in a specialty pharmacy with an integrated care model.¹⁶ However, our study utilized the MPR to measure adherence, whereas Shah et al utilized the proportion of days covered.

The first contact that a patient has with a health care provider offers the patient an opportunity to talk and ask questions and allows the provider to understand the patient's individual needs in terms of disease state and therapy-specific information. Too much information may be overwhelming,¹⁷ and patients may vary in the degree to which they benefit from participation in patient education.¹⁸ Providers must gauge what level of information is appropriate and how much information the patient can process and retain at different stages of their disease. Our nursing program was designed with these considerations and includes follow-up visits during the titration phase of therapy to reinforce side effect management and adherence. Additionally, we provide a patient assessment to gather insight into how the patient progresses with their current therapy. Each patient assessment is completed by a PAH-trained CVS Health nurse and is a comprehensive assessment that includes, but is not limited to, evaluating medication side effects, tolerability, and changes in activities of daily living. This assessment is used to help nurses better understand the needs of individual patients and stimulate discussions specific to each patient; this assessment is also shared with the patient's PAH provider.

This study is not without its limitations. First, we compared three different therapy classes, prostacyclin and soluble guanylate cyclase stimulators versus ERAs, which have different side effects and tolerability profiles and patients in different functional classes. The ideal study design would have compared patients on prostacyclin or riociguat therapies receiving and not receiving the nursing intervention; however, the patient sample was insufficient to power this study design. Second, this study used pharmacy claims without access to the medical claims; thus, we could not confirm the diagnosis of PAH via medical claims or chart records. Third, pharmacy refill records might not reflect actual consumption. In our study, the fill count was higher in the study group than in the control group. This finding may relate to adherence or may have been skewed given the more complicated titrated dos-

ing of the therapies within study group, as compared the the ERA class. Fourth, we evaluated patients for only 6 months; the results from our study might not be generalizable to longer periods. Future studies should attempt to confirm the findings using a longer evaluation period. Additionally, other unknown confounders may exist, which could result in biased estimates. Due to the single-site, non-randomized, retrospective design of this study, we can interpret the results only as associative rather than causative. The results of this study may not be generalizable to the general PAH population.

CONCLUSIONS

Patients receiving oral PAH therapies (riociguat, selexipag, or treprostinil) supported through a visiting nurse program had significantly higher rates of optimal adherence as demonstrated by a statistically significant improvement in the MPR and a higher prescription fill count than a control group. A multidisciplinary approach supporting the patient and providing patient education, proper motivation, and face-to-face nursing may support improved patient outcomes.

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