Pulmonary arterial hypertension (PAH) is a severe, complex, and rare disease. It is characterized by vascular remodeling of the pulmonary arteries which carry blood from the heart to the lungs. This leads to a progressive increase in pulmonary vascular resistance that leads to right ventricular failure and significant morbidity and mortality. PAH incidence and prevalence rates vary significantly. Registry-based estimates vary from 2.3–7.6 patients per million and 15 to 26 patients per million, respectively. Patients with PAH typically experience dyspnea on exertion, fatigue, chest pain, syncope, and peripheral edema. Furthermore, they often have multiple comorbidities, such as systemic hypertension, obesity, connective tissue disease, sleep apnea, and diabetes.

The 6th World Symposium on Pulmonary Hypertension Task Force on hemodynamic definitions and clinical classifications defined pulmonary hypertension (PH) as a mean pulmonary artery pressure at rest of >20 mmHg, confirmed by right heart catheterization and a pulmonary vascular resistance of ≥3 Wood units. The current guidelines from the European Society of Cardiology/European Respiratory Society classify PH into 5 diagnostic categories by shared pathobiology and pathophysiology.

As seen in Figure 1, PH group 1, PAH, is further divided into 7 subcategories. Although this framework helps categorize patients and inform treatment decisions, patients with PH may present and respond to treatment differently based on their risk status, risk factors, and comorbidities. Diagnostic and treatment strategies for patients with PH must be developed on an individual basis, driven by a provider’s knowledge of each patient’s specific needs.

PAH Treatment Journey

Diagnosis of PAH

Practitioners and patients face difficulties in identifying and diagnosing PAH because it requires a clinical suspicion based on symptoms, a physical examination, known risk factors, and/or incidental findings on tests ordered for other purposes. Evaluation to detect the presence of PH and determine whether a patient also has PAH requires a comprehensive set of tests, which typically

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Ensuring Appropriate Access to Pulmonary Arterial Hypertension Therapy

Kristin B. Highland, MD, MSCR; Kathleen E. Hughes, MBA; Kenneth J. Williams, MA, MBA; Brigit Kyei-Baffour, MBA; Samantha Ferguson

ABSTRACT

Pulmonary arterial hypertension (PAH) is a progressive, complex disease. PAH is a type of pulmonary hypertension (PH) and can be further categorized into 7 subdivisions, representing a variety of causal and phenotypic factors. Patients with PH, including PAH, are typically fragile and experience multiple comorbidities; they therefore require individualized treatment plans based on their risk status and etiology. Based on a review of clinical evidence, a wide variety of treatment options exist for PAH, including general measures (eg, physical activity and oral anticoagulants), nonspecific pharmacologic intervention (eg, calcium channel blockers), and targeted pharmacologic intervention. Guidelines point to a flexible approach, frequently including upfront or sequential combination therapy, to mitigate disease progression. Payer-driven drug exclusion policies, including formulary restrictions and noncoverage policies, can detract from the ability of providers to offer treatments consistent with guidelines, as they limit access to the range of treatment options needed for individualized patients. Providers must be able to work with each patient to develop a tailored strategy through open access to treatments, leveraging all available options, to mitigate against exacerbation of comorbidities and optimize care.


For author information and disclosures, see end of text.
include laboratory testing, echocardiography, pulmonary function testing, assessment of exercise capacity with six-minute walk distance (6MWD) or cardiopulmonary exercising testing (CPET), imaging (chest x-ray, chest computed tomography scan, cardiac magnetic resonance [CMR] imaging, ventilation/perfusion lung scan), nocturnal oximetry and/or overnight polysomnography, and right heart catheterization (Figure 2). Some patients also require pulmonary angiography or left heart catheterization with angiography. Together, these tests confirm the presence of PH, allow patients to be categorized into one of the 7 PAH groups, and may lead to further identification of the underlying disease etiology. These tests are also used to stratify patients by "risk level" for clinical worsening, which further informs treatment decisions.

This extensive testing, which is required to positively diagnose a patient with PH, frequently necessitates referral to a PH center or expert—particularly since clinical presentation can be complicated by individual patient characteristics and comorbidities. On average, patients report visiting their primary care provider more than 5 times and being referred to 3 specialists before being referred to a PH expert, resulting in an average delay of 47±34 months from symptom onset to diagnosis by right heart catheterization. This delay is associated with a deterioration of patients' functional status, which is, in turn, associated with increased mortality.

Retrospective data from a French regional referral center revealed that the median overall long-term survival post-diagnosis for PAH is 46.0±1.4 months, which may be worsened by delayed diagnosis and/or a greater number of comorbidities. Conversely, early diagnosis and access to effective treatment can contribute to improvement in survival rates. The Registry to Evaluate Early and Long-Term Pulmonary Arterial Disease Management (REVEAL) was initiated in the United States in 2006 to better understand the clinical course, treatment, and predictors of outcomes in patients with PAH. The REVEAL data demonstrated an almost 3-fold improvement in patient survival rates compared with results gathered nearly 3 decades ago from the National Institutes of Health PAH registry, which followed 194 patients in the 1980s as the first PAH registry. The authors of this analysis suggest that the considerable improvement in survival rates could be attributed to a combination of factors, including changes in treatments and improved patient-support strategies.

**Assessment of Disease Severity**

Assessment of patients’ risk status is a key component of the PAH treatment strategy, allowing clinicians to predict survival, monitor disease progression, and inform treatment decisions. The 2015 European Society of Cardiology/European Respiratory Society PH guidelines, which include treatment guidelines for PAH, link treatment approaches for individual patients to an assessment of patients’ “risk” for clinical worsening and 1-year mortality based on clinical status, functional status, exercise, right ventricular function, and hemodynamic parameters. The guidelines categorize patient risk into low-, medium-, or high-risk categories based on anticipated 1-year mortality. In 2018, researchers validated the connection between methodical risk assessment and treatment strategy through retrospective analysis of 3 independent registries, demonstrating that a multiparametric approach could predict survival or event-free survival. Each registry—REVEAL, the Swedish PAH Register, and COMPERA—defines parameters for low-risk PAH based on a scoring algorithm and assesses 1-year mortality by risk group, with individual risk assessed at baseline and first follow-up (Table 1).

Provider assessment of patients’ status incorporates a multidimensional approach, including findings of right heart failure on physical examination, laboratory values (creatinine, N-terminal pro brain natriuretic peptide, or brain natriuretic peptide), World Health Organization (WHO) functional classifications, exercise testing (6MWD, CPET), progression of symptoms, echocardiography, CMR imaging, syncope, and hemodynamics. These tests are
ENSURING APPROPRIATE ACCESS TO PULMONARY ARTERIAL HYPERTENSION THERAPY

**FIGURE 2.** Pulmonary Arterial Hypertension Diagnostic Algorithm

- Symptoms, signs, history suggestive of PH
  - Echocardiographic probability of PH
    - High or intermediate
    - Low

- Consider left heart disease and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases
- No signs of severe PH/RV dysfunction
  - Treat underlying disease
- Signs of severe PH/RV dysfunction
  - V/Q scan
  - Mismatched perfusion defects?
    - Yes
      - Refer to PH expert centre
    - No
      - RHC (Table 10)
        - mPAP ≥25 mmHg, PAWP ≤15 mmHg, PVR >3 Wood units
        - CTEPH possible:
          - CT pulmonary angiography, RHC +/- pulmonary angiography
          - No
            - Refer to PH expert centre
          - Yes
            - PAH likely
              - Specific diagnostic tests
- Group 5
  - CHD
  - Drugs - toxin
  - PVOD/PCH
  - PAH
  - Heritable PAH

CHD indicates congenital heart diseases; CT, computed tomography; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, carbon monoxide diffusing capacity; ECG, electrocardiogram; HIV, human immunodeficiency virus; HR-CT, high resolution CT; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PFT, pulmonary function tests; PH, pulmonary hypertension; PVOD/PCH, pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis; PVR, pulmonary vascular resistance; RHC, right heart catheterisation; RV, right ventricular; V/Q, ventilation/perfusion.

Figure recreated with permission from Galíé N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Respir J. 2015;46:903–975.
performed regularly to monitor patient prognosis and guide treatment decisions beyond initial determination of risk. Furthermore, the guidelines specify that no one variable may be used to determine risk; instead, providers must make a comprehensive assessment of each individual patient, incorporating rate of disease progression, comorbidities, age, sex, background therapy, and PAH subtype in addition to the modifiable parameters listed previously.3

Because of the unique patient profiles of those with PAH, a “one size fits all” treatment paradigm will not result in optimal care. The unique characteristics of each patient’s profile warrants a tailored treatment approach that considers the impact of each patient’s characteristics on responsiveness to treatment and symptom improvement.

### PAH Treatment Options

Following diagnosis and assessment of disease severity, a wide variety of treatment options exist for patients with PAH, ranging from general measures to targeted pharmacological interventions.3 The treatment approach for patients with PAH can be summarized in the following algorithm, which is aligned with the most recent treatment guidelines:

#### General Measures

Patients should adopt general measures (e.g., physical activity, supervised rehabilitation, infection prevention, psychosocial support), initiate supportive therapy (e.g., oral anticoagulants, diuretics, oxygen, and digoxin), and be referred to a PH expert center.

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**TABLE 1. Summary of 4 Registries Assessing Risk Scores15**

<table>
<thead>
<tr>
<th>Criteria Used to Classify Risk</th>
<th>REVEAL</th>
<th>Swedish PAH Register</th>
<th>COMPERA</th>
<th>French Pulmonary Hypertension Network</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal insufficiency</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sex</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Age</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Functional class</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Heart rate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>6-minute walk distance</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Brain natriuretic peptide or N-terminal pro brain natriuretic peptide</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Right atrial pressure or mean right atrial pressure</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Imaging (echocardiography)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Right atrium area</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>1-year mortality</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Additional Registry Characteristics**

<table>
<thead>
<tr>
<th>Number of patients at follow-up</th>
<th>2529</th>
<th>383</th>
<th>1094</th>
<th>1017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numerical risk values</td>
<td>-2 to +2</td>
<td>1 = low; 2 = intermediate; 3 = high</td>
<td>1 = low; 2 = intermediate; 3 = high</td>
<td>0-4 affiliated low-risk criteria</td>
</tr>
<tr>
<td>Definition of low risk</td>
<td>≤6 REVEAL score</td>
<td>&lt;1.5 average score</td>
<td>&lt;1.5 average score</td>
<td>3-4 out of 4 low-risk criteria</td>
</tr>
<tr>
<td>1-year mortality rates by risk group (low/intermediate/high), %</td>
<td>≤2.6/7.0/≤10.7</td>
<td>1.0/7.0/26.0</td>
<td>2.8/9.9/21/2</td>
<td>1.0/NA/13.0-30.0</td>
</tr>
</tbody>
</table>

PAH indicates post arterial hypertension.

Pharmacologic Measures

- **Non-PAH-specific therapy:** After diagnosis of PAH, acute vasoreactivity testing should be performed to predict responsiveness to calcium channel blockers (CCBs).*
- **PAH-specific therapy:** Five classes of PAH-specific therapy are available to patients with PAH (Table 2). The guidelines provide an overview of use.

**Oral Combination Therapy**

Patients who are nonvasoreactive and vasoreactive without an adequate treatment response to CCBs who are at low or intermediate risk should be treated initially with an endothelin receptor antagonist (ERA) and a phosphodiesterase-5 inhibitor. These drugs may be initiated concomitantly or in rapid sequence. In patients who are nonvasoreactive and treatment-naïve at high risk, initial combination therapy is recommended. Combinations that include a parenteral prostanoid receive the strongest recommendation, although other combinations may be considered according to individual patient needs. There also should be a low threshold for referral for lung transplantation.

**Oral Monotherapy with PAH-Specific Agents**

Combination therapy may not be appropriate for patients with PAH who have certain comorbidities (eg, patients aged >75 years with idiopathic PAH and multiple risk factors for left heart failure, patients with severe liver disease); these patients should be treated with monotherapy. As there have been no head-to-head clinical trials, the choice of drug may depend on a variety of factors, including approval status, labeling, route of administration, adverse effect profile, potential interaction with background therapies, patient preferences, comorbidities, physician experience, and cost.

**Continued Pharmacologic Therapy**

When the initial treatment approach results in a low-risk status within 3 to 6 months, the therapy should be continued. When the initial treatment approach results in an intermediate-risk status, escalation to triple combination therapy is recommended (or double combination if monotherapy was initially selected). When the initial treatment approach results in a high-risk status, maximal medical therapy is recommended. Referral for lung transplantation should also be considered.

**Procedural Intervention**

Lung transplantation should be considered if the patient is refractory to maximal medical therapeutic intervention. Balloon atrial septostomy should be regarded as a palliative or bridging procedure in patients who are deteriorating despite maximal medical therapy.

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* Based on the 2009 ACC/AHA and 2015 ESC/ERS guidelines, only those that demonstrate reduction in the mean pulmonary artery pressure of at least 10 mmHg to an absolute mean PA pressure of less than 40 mm Hg with a stable or improved cardiac output post vasodilator administration during right heart catheterization may be treated with progressively titrated doses of CCBs.
of efficacy. In 2011, results from a meta-analysis suggested that combining therapies did not offer any advantage over monotherapy, except for a modest increase in exercise capacity. Combination trials included in this meta-analysis were mainly short-term and assessed the 6MWD as the primary efficacy endpoint. Since then, the results of numerous studies of longer duration and using a “time-to-clinical-worsening endpoint,” a composite of outcomes consisting include death, admission to hospital, treatment escalation, transplantation, atrial septostomy, and PAH worsening, have been published and analyzed. While the 6MWD is included as a clinical endpoint in some recent analyses, the “time-to-clinical-worsening endpoint” may be considered a superior indicator for efficacy as it conveys the overall health status of a patient rather than a proxy indication for functional ability.

For a 2016 meta-analysis, researchers examined the literature for prospective, randomized, controlled trials of at least 12 weeks’ duration performed between 1990 and 2015. They were looking for trials comparing combinations of approved PAH-targeted therapies with monotherapy and reporting on a primary outcome of interest (clinical worsening) or 1 or more secondary outcome (all-cause mortality, PAH-related mortality, PAH-related admission to hospital, lung transplantation, treatment escalation, symptomatic progression, changes in WHO functional class, treatment discontinuation, and treatment duration). Seventeen studies (4095 patients) were included demonstrating that combination therapy significantly reduced the risk of clinical worsening compared with monotherapy (risk ratio 0.65 [95% CI 0.58–0.72], P < .00001). This effect was consistent across subgroups, including drug classes, study duration and design, and patients’ characteristics. Combination therapy was also associated with an enhanced improvement in patients’ functional status. This 2016 meta-analysis included a substantial proportion of studies of longer duration using clinical worsening as a primary endpoint and supported the effect of combination therapy on clinically relevant outcomes in PAH.

Combination therapy, either upfront or sequential, has become the standard of care in PAH for appropriate patients. The above-cited meta-analyses provide strong evidence supporting this treatment strategy, which has been codified over time in treatment guidelines. Registry data support the real-world use of findings from the clinical trial results and guidelines. A 2012 analysis of data from REVEAL found that 46% of patients with PAH are being treated with dual agents and 9% are on triple therapy.

Notable from the research, and reflected in the guidelines, is the fact that while many patients benefit from combination therapy, some do not, which supports the notion that monotherapy options should be maintained for appropriate patients. Perhaps more importantly, a substantial proportion of patients with PAH in the clinical trials had clinical worsening despite combination therapy. This underscores the need for the identification of innovative new therapeutic targets in PAH treatment development, with allowances being made for open access to “creative” patient-specific therapies in the interim.

### PAH Disease and Economic Burden

Patients with PAH demonstrate significant healthcare resource utilization. The annual pharmacy costs of patients with PAH are 17 to 21 times higher than the average Medicare part D patient, and the average annual medical costs for patients with PAH are 10 to 11 times the costs of the average Medicare patient.

Hospitalization, a frequent occurrence in patients with PAH, can represent a significant financial burden for patients, their caretakers, and their health plans. A claims analysis of data from a nationally representative database demonstrated that 79.3% of hospitalized patients with PAH were re-hospitalized within 1 year of discharge, with approximately 1 in 5 patients returning to the hospital within 30 days of discharge. Averaged among patients with at least 1 PH-related hospitalization, the mean hospitalization cost totaled $46,118; SD = $135,137, while readmission costs totaled $35,188; SD = $152,006. As a basis for comparison with another well-studied, expensive condition, PAH costs were significantly higher than the mean heart failure–related hospitalization costs, even when adjusting for inflation, which totaled $31,998 for initial hospitalization and $24,839 for readmissions.

The readmission rates for patients with PAH reported above are similar to the 30-day readmission rates seen in congestive heart failure, acute myocardial infarction and chronic obstructive pulmonary disease, all of which are targeted by programs, such as CMS’ Hospital Readmissions Reduction Program, as areas to decrease healthcare costs. The conditions listed in Table 4 frequently occur as comorbid conditions for patients with PAH, which often contribute to higher-than-average hospital inpatient stays.

In addition, PH-associated diagnosis codes are included in CMS’ list of major complications and comorbidities, which results in assignment of patients to the more severe variants in diagnosis-related group (DRG) triplets (as applicable). Higher hospital reimbursement rates reflect the higher costs to treat patients assigned these DRG variants.

### Table 4: Thirty-Day Readmissions Rate PAH Comparison

<table>
<thead>
<tr>
<th>Category</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>National average</td>
<td>14%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>25%</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>20%</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>19%</td>
</tr>
<tr>
<td>PAH</td>
<td>21%</td>
</tr>
</tbody>
</table>

PAH indicates pulmonary arterial hypertension.

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In addition to the economic burden of hospitalizations, PAH-specific pharmacologic therapies also pose substantial costs, with wholesale acquisition costs ranging from $25,000 to $250,000 for “average dosing.” While these prices have contributed to growing payer interest in cost control using techniques, such as prior authorization, tiered use, and formulary restrictions, costs offsets could be achieved by early diagnosis and targeted therapies. A 2017 literature review of healthcare economic publications examining the cost burden of PAH and the impact of some specific therapies found that the clinical benefit of early intervention and combination therapy for PAH could offset the costs by reducing hospitalizations. The literature review examined data from various databases for studies comparing drug cost, clinical outcomes, and hospitalization burden associated with therapy for PAH. Early first-line combination therapy demonstrated significant benefit in reducing mortality rates as well. One economic model, assuming 1 million health plan members showed a 15% decrease in total costs over baseline after 2 years for patients who were treated with approved PAH pharmaceutical therapies—corresponding to a cost savings of $0.04 per member per month.\(^{11}\)

As treatment guidelines and patterns of PAH care continue to evolve, the need for comprehensive budget impact models reflecting contemporary patterns of care increases. In particular, the need to fairly assess the other health resource utilization offsets that may come from pharmacologic treatment that is individualized to the needs of patients with PAH is imperative, particularly given the high cost of the condition.

### Appropriate Access Considerations

It is essential that physicians be able to make tailored treatment decisions for individual patients, given the complex and heterogeneous nature of PAH.\(^{2}\) Current guidance recommend that the “optimal therapeutic approach” for each patient must be individualized to account for “severity of illness, route of administration of therapy, side effect profile, comorbid illnesses, treatment goals, and clinician experience and preference.” As such, patients require access to all indicated treatment options to optimize disease management.\(^{3}\)

As has been described previously, the recommended PAH treatment strategy begins with appropriate diagnosis, assessment of functional status and risk, and access to physician-directed treatment.\(^{4}\) To identify the optimal treatment path, physicians consider patient-specific factors (eg, background therapy, comorbidities, age, sex, etiology of PAH, social support) to avoid harm and increase the likelihood of quickly identifying an effective treatment regimen. Rapid access to appropriate treatment is essential for patients with PAH given the progressive nature of this disease. Delays in achieving an optimal treatment regimen have been associated with deterioration in functional class, which 1 study confirmed as a predictor of mortality.\(^{12,13}\) Multiple regimens may be necessary to determine an effective treatment regimen necessitating having more than “just one choice” for treatment.\(^{12}\) Figure 3 provides examples from real-life cases.

As supported by clinical trial work and evolving guidelines, treatment needs will vary by patient—some patients may not be able to tolerate certain medications, while others may be more

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**FIGURE 3. Real-Life Patient Case Examples**

- A 72-year-old woman with idiopathic pulmonary arterial hypertension (PAH) had been stabilized on parenteral prostanoid therapy for approximately 10 years. She developed early onset Alzheimer disease and began making mistakes mixing her medication and operating her pump, which resulted in several hospitalizations. She was successfully transitioned to an oral agent that worked on the prostanoid pathway.

- A 54-year-old woman with idiopathic PAH was unable to remember to take her PAH medication 3 times daily. She continued to decline in her 6-minute walk distance and functional status, as well as having an elevation in her N-terminal probrain natriuretic peptide. She was changed to a once-daily formulation with rapid improvement in disease markers.

- A 52-year-old woman with very severe scleroderma-associated PAH developed worsening hypoxemia on oral therapies. The addition of an inhaled PAH medication allowed for treatment of her PAH with preservation of ventilation/perfusion matching.

- A 68-year-old man with long-standing idiopathic PAH developed concomitant diastolic dysfunction and worsening lower extremity edema. The changing of one endothelin receptor antagonist to another improved this adverse effect.

- A 30-year-old woman with scleroderma-associated PAH was initially started on an endothelin receptor antagonist (ERA) and once-daily branded PDE5i. She received co-pay assistance from the pharmaceutical companies for her medications. Her insurance company required her to change to a generic sildenafil. She had difficulty adhering to 3-times-daily dosing and ultimately self-discontinued therapy due to a lack of co-pay assistance. She developed progressive right heart failure and required resuming with a parenteral prostanoid.

- A 43-year-old woman with idiopathic PAH was started on generic epoprostenol. There was a shortage of this formulation of epoprostenol. There was an interruption in her therapy while she awaited approval of brand epoprostenol. During this time, she developed acute right heart failure and required admission to the intensive care unit.

- A 57-year-old man with idiopathic PAH was started on generic epoprostenol. He was transitioned to the same dose of brand epoprostenol during the generic shortage and developed hypotension requiring a brief hospitalization. Hemodynamics returned to baseline after brand was reduced by 5 ng/kg/min.
responsive to different options. Given the progressive nature of PAH, the importance of early treatment, and the need for individually tailored treatment decisions, it is essential that patients with PAH and their providers have access to all treatment options to allow for the best possible outcomes.

**Provider-Patient Choice**

As discussed previously, there has been an evolution in the PAH treatment guidelines. This has been precipitated by more robust clinical trials, as well as informed by real-world practice over time. These significant findings and other beneficial changes to treatment pathways were enabled through open access to therapy and provider-patient real-world use.

Restrictive payer management strategies may have had unintended negative outcomes on patients with certain comorbidities in addition to the primary diagnosis of PAH. This phenomenon is particularly true for patients with orphan conditions, such as PAH, because of small patient numbers and limited clinical understanding of evolving evidence on treatment options. For example, if patients are required to move through step therapies, a common payer cost-containment technique, many patients may never recover the time lost to disease progression and/or may experience increased complications due to comorbidities. This is highlighted in PAH by the lack of "catch-up" in the previously treated placebo group patients in all of the open-label extension trials that have been performed in PAH. Furthermore, given its now-prominent place in PAH treatment guidelines, "early first-line combination therapy" for the right patients has demonstrated "significant benefit" in terms of mortality, hospitalizations, and disease progression. Often, patients with PAH who are treated initially with monotherapy will need to escalate to dual or triple combination therapy, which also has been shown to reduce hospitalizations and improve patient outcomes in clinical trials in comparison to remaining on monotherapy. Formulary exclusions may also add an additional layer of challenge when navigating drug shortages, particularly when treating such fragile patients.

Payers need to maintain flexibility in making policy decisions on treatments for patients with orphan conditions, specifically PAH, to create an environment in which knowledge of the disease, its treatment, and economic impact can continue to evolve.

**Impact of Drug Exclusion Policies**

Drug exclusion policies are generally put in place with the intent of lowering costs without adversely affecting quality of care. However, in a review of the impact of utilization management strategies, researchers found that roughly 20% of drug exclusion policies increase costs, typically due to increased expenditure for other healthcare services, and 25% negatively impact patients. Specific to PAH, drug exclusion policies may deter providers from the early initiation of combination therapy, which is known to reduce morbidity, mortality, and healthcare resource utilization.

Furthermore, since the treatment strategy for PAH is specific to individual patients, utilization management may result in nonmedical switching, which could have a negative effect on these patients. A systemic literature review of patients with 6 disease conditions (cardiometabolic, immune-mediated, acid suppression, psychiatric, hormone replacement therapy, and pain) demonstrated that the nonmedical switching experienced by patients was negatively associated with clinical, economic, healthcare utilization, and medication-taking behavior outcomes, which may also be applicable to patients with PAH. Similar inferences can be made from a 2007 review of 41 studies examining the effects of formulary restrictions. The results of the study found that closed formularies have been associated with "lower rates of medication continuation among patients with chronic conditions," and some studies reviewed therein even found that "limiting coverage to generic drugs was associated with decreased medication use and increased hospitalizations." The review also confirmed that utilization management strategies affect fragile patient populations with complex chronic conditions, including congestive heart failure, more severely than patients with other common disease states. The fragility and comorbid nature of patients with PAH may mean that utilization management strategies have a disproportionately negative effect on them, further highlighting the critical need for open access.

The literature provides many historic examples of potential risks of formulary restrictions to demonstrate "unintended consequences on patient or payer outcomes." For one, a review of state policies restricting access to pregabalin for diabetic peripheral neuropathy and postherpetic neuralgia showed that patients for whom access was restricted experienced "significantly greater disease-specific costs" and increased probability of the use of opioids, analgesics, tricyclic antidepressants, and anxiolytics. Drug costs cannot be considered alone in analyzing unintended negative effects of exclusionary drug policies, particularly when treating complex diseases such as PAH. Finding many analyses dated, an important professional society emphasized that such analyses “should be based on accurate and up-to-date clinical criteria,” as well.

Noncoverage policies frequently lead patients to file for medical exception and go through appeals processes, adding unnecessary time and administrative costs for stakeholders. Eighty-four percent of physicians report that the burden associated with utilization management is high or extremely high—especially as 79% of physicians report that they are required to resubmit appeals for repeated prescriptions to treat chronic conditions such as PAH.

Exclusion policies and burdensome utilization management policies detract from the ability of providers to offer individualized treatment strategies for patients with PAH. Providers must retain the ability to work with patients in an individual capacity.
to identify treatment strategies that increase the likelihood of achieving better outcomes.

Conclusions

Patients with PAH are fragile and often have multiple comorbidities requiring individually tailored treatments to optimize outcomes. The treatment options for PAH have evolved significantly, resulting in a positive impact on morbidity and mortality. However, considering the rapid disease progression associated with PAH and the limited availability of data on the treatment of patients with PAH who have significant comorbidities, restricted access to a wide variety of treatment options could significantly impact outcomes. To provide optimal care for patients and minimize disease progression, the provider and patient must have the ability to customize treatment using all available treatment choices.

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