A Supplement to CareManagement

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Accessing Pulmonary Arterial Hypertension (PAH) Medication—It Takes a Village!

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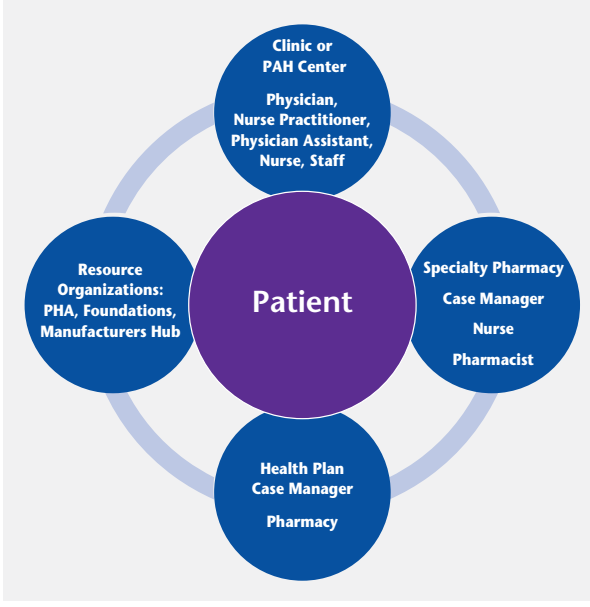
Pulmonary arterial hypertension (PAH) is a rare, chronic disease that often leads to disability and premature death. In PAH, proliferation of the endothelium of the pulmonary arterioles and smooth muscle cell hypertrophy cause narrowing of the vessel lumen. This leads to increased pulmonary vascular resistance, right ventricular remodeling and dysfunction, and ultimately, right heart failure. The average life expectancy after diagnosis is approximately 7 years,[1] up from 2.5 years[2] a couple of decades ago. In part, this progress is due to the availability of newer pharmacologic agents. However, even with multiple treatments available, the 1-year mortality rate is 15%.[1] Currently there are 13 FDA-approved drugs available (Table 1) with four new agents approved in the last 4 years. Given the severity of the disease, timely access to these important medications is critical.

FIGURE 1 THE PATIENT AT THE CENTER



The Patient and Provider Team

The patient must be an integral part of the treatment team practicing patient-centered care (Figure 1). Guiding clinical decisions with patient-centered care demonstrates respect for the patient.[3] Achieving shared decision-making requires developing a good relationship between the patient and care team, sharing information, and supporting patients in expressing their preferences and views in the decision-making process.[4] Some decisions are straight forward (ie, a hip fracture needs repair), but for most medical decisions, there is more than one reasonable option.[3] These different options entail different combinations of possible therapeutic effects and side effects.[3] For example, some PAH medications (treprostinil, epoprostenol) are administered through the parenteral route, requiring titration and may necessitate central line placement with concomitant potential for local and systemic infections. Some newer oral medications (selexipag, orenitram, riociguat) require titration to therapeutic levels over weeks to months. Patient input and buy-in are important in selecting and prescribing therapeutic options and may play a role in medication adherence.

The patient is not alone through the PAH journey. Numerous resources exist, including professionals in centers or clinics, health plans, and specialty pharmacies, as well as the Pulmonary Hypertension Association (PHA), patient support groups, and manufacturer-sponsored educational materials and programs. Patients who are technologically savvy have an advantage because they are not only able to access the myriad online educational resources, but can find out what financial resources become available and apply quickly for them, often ahead of others who may not have access to computers. Patients who access the varied resources can partner most effectively with the health care team.

Pharmacologic Treatment

Currently, there are FDA-approved drugs targeting three known pathways that contribute to the development of PAH. Selection of appropriate drugs must be individual-

TABLE 1 **PULMONARY ARTERIAL HYPERTENSION MEDICATIONS**

Pathway	Classification	Medication Generic (Brand)	Administration Route
Prostacyclin	Prostacyclin	epoprostenol (Flolan®)	IV - Central Line
	Prostacyclin	epoprostenol for injection (Veletri®)	IV - Central Line
	Prostacyclin	epoprostenol sodium (generic of Flolan® for Injection)	IV - Central Line
	Prostacyclin analog	treprostinill* (Remodulin®)	IV/Subcutaneous
	Prostacyclin analog	iloprost (Ventavis®)	Inhaled
	Prostacyclin analog	treprostinil (Tyvaso®)	Inhaled
	Prostacyclin analog	treprostinil (Orenitram®)	Oral
	Selective IP receptor agonist	selexipag (Uptravi®)	Oral
Endothelin	Endothelin-receptor antagonist	bosentan (Tracleer®)	Oral
	Endothelin-receptor antagonist	ambrisentan (Letairis®)	Oral
	Endothelin-receptor antagonist	macitentan (Opsumit®)	Oral
Nitric Oxide	PDE5 inhibitor	sildenifil (Revatio®)	Oral
	PDE5 inhibitor	generic sildenafil**	Oral
	PDE5 inhibitor	tadalifil (Adcirca®)	Oral
	Soluble guanylate stimulator	riociguat (Adempas®)	Oral

* treprostinil is available as parenteral, inhaled, and oral forms. ** generic sildenafil is available through more than one manufacturer.

Flolan® (epoprostenol) Prescribing Information. Brentford, UK: GlaxoSmithKline; June 2016.

Veletri® (epoprostenol for injection). Prescribing Information. Brisbane, CA: Actelion Pharmaceuticals US, Inc.; July 2016.

Generic of Flolan® for Injection (epoprostenol sodium). Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA, Inc.; August 2017.

Remodulin® (treprostinil). Prescribing Information. Silver Spring, MD: United Therapeutics Corp.; December 2014.

Ventavis® (iloprost). Prescribing Information. Brisbaqne, CA: Actelion Pharmaceuticals US, Inc.; October 2017.

Tyvaso® (treprostinil). Prescribing Information. Silver Spring, MD: United Therapeutics Corp.; October 2017.

Orenitram® (treprostinil). Prescribing Information. Silver Spring, MD: United Therapeutics Corp.; January 2017.

Uptravi® (selexipag). Prescribing Information. Brisbane, CA: Actelion Pharmaceuticals US, Inc.; December 2017.

Tracleer® (bosentan). Prescribing Information. Brisbane, CA: Actelion Pharmaceuticals US, Inc.; September 2017.

Letairis® (ambrisentan). Prescribing Information. Foster City, CA: Gilead Sciences Inc.; October 2015.. Prescribing Information. Actelion Pharmaceuticals US, Inc.; September 2017

Opsumit® (macitentan). Prescribing Information. Brisbane, CA: Actelion Pharmaceuticals US, Inc.; March 2017.

Revatio® (sildenafil). Prescribing Information. Groton, CT: Pfizer Labs.; July 2017.

Adcirca® (tadalifil). Prescribing Information. Indianapolis, IN: Eli Lily and Company. August 2017.

Adempas® (riociguat). Prescribing Information. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; January 2018.

ized; prescribers must consider factors such as stage of disease, comorbidities, support systems, and potential patient response because all patients will not respond to a medication in the same way. Thus, it is important that prescribers have access to the entire armamentarium of PAH medications. The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension recommend risk stratification to guide medication selection. Patients are classified as low, intermediate, or high risk for clinical worsening or death. Low-risk patients present with nonprogressive disease (functional capacity [FC] I or II), 6-minute walking distance (6MWD) greater than 440 m, no signs of clinically relevant right ventricular (RV) dysfunction; and have an estimated 1-year mortality risk of 5%. Intermediate-risk patients present in FC III, and have moderately impaired exercise capacity, signs of RV dysfunction, and a 1-year mortality risk of 5% to 10%. High-risk patients have estimated 1-year mortality risk greater than 10% and present in FC III or IV with progressive disease, signs of severe RV dysfunction or failure, and secondary organ dysfunction.[5]

Physicians make choices within each class of drugs and may use a drug that acts on more than one pathway to tailor their patient's medication regimen. Combination therapy

can be prescribed as initial or sequential. Combination therapy allows targeting more than one of the three implicated signaling pathways—prostacyclin, endothelin, and nitric oxide.[5] It is recommended as initial or sequential therapy to help patients achieve low-risk status. Some combinations require special considerations. For example, riociguat is contraindicated with a phosphodiasterase 5 (PDE5) inhibitor because of the risk of dangerous hypotension, and ambrisentan in combination with tadalafil is associated with increased edema.

Accessing PAH Medication: The Village

Prescriber Office

When the patient is diagnosed, the provider team (physician, NP/PA, case manager, nurse, social worker) has an important role in orienting the patient to their new health state. A PAH diagnosis creates anxiety for the patient as they become knowledgeable about it being a chronic life-threatening disease. Adjusting to a new state of health and accepting a new "normal" requires the support and education of patient and family. The PAH team provides education about the disease, treatment goals, therapies, ongoing assessment, support, and resources. This process necessarily begins at diagnosis and continues over the course of the disease. Beginning or adding a PAH therapy can be a complex process and once the health care provider and patient decide on a treatment, "getting the medication" becomes important.

Frequently, patients require financial assistance to purchase their drug(s). Accessing financial assistance may begin in the provider office. There are a number of foundations that offer assistance, but their money is exhausted quickly. The beginning of the calendar year poses additional challenges as changes to patients' health plans may require patients to apply or reapply for financial assistance. An astute and caring team within the prescriber office is instrumental in helping the patient to access these funds.

In the clinic or PAH center, an enrollment form is completed, as needed, for PAH therapy. This can be done by the prescriber, nursing staff, medical assistants, or support staff. The enrollment form may contain information on medical necessity and Risk Evaluation and Mitigation Strategy (REMS), if applicable. Other important information includes the signed prescription and patient consent for treatment and necessary information sharing. An initial obstacle to the process may be incompleteness of the enrollment form or the REMS requirement. Frequently, signatures—patient or provider—are missing, which can lead to delays in processing the medication request. The enrollment form is forwarded either to a hub or directly to the specialty pharmacy.

Manufacturer-Sponsored Services—Hub

The majority of the enrollments are processed through the hub, which may be within the manufacturing organization or through a third-party vendor. The hub performs a number of important functions. The first step involves entering the enrollment data into a secure database.

Next, the completed form goes to a case manager where the benefits verification process begins for patients who have provided their consent. Insurance plan coverage, costs, copay information, and need for a prior authorization (PA) are assessed. Almost all specialty medications, including PAH-specific medications, require a PA. A case manager may provide education and information related to health plan policies to the physician's office. The PA process enables the patient to obtain the medication when its indication is supported by scientific evidence that demonstrates its benefit. For example, with the exception of riociguat, all PAH medications are approved for World Health Organization (WHO) group I patients only. (These are patients with pulmonary arterial hypertension.) Therefore, hemodynamic parameters that demonstrate that the patient does, in fact, have PAH are critical. A right heart catheterization (the gold standard for diagnosis) is usually required. The hemodynamic definition for PAH is pulmonary artery pressure (PAP) of 25 mm Hg or higher, pulmonary vascular resistance (PVR) greater than 3 Woods units, and pulmonary artery wedge pressure (PAWP) of 15 mm Hg or less.

According to one source, every year 185 million prescriptions[6] go unfilled because the PA is denied. A number of companies allow the PA to be submitted electronically at the point of prescribing and then send immediate feedback about approval. A number of large insurers and provider offices are currently using these systems successfully, which predicts that the electronic PA may become mandatory in a few years, perhaps shaving days off the process and getting the medication to the patient more quickly.

Sometimes, a PA is not approved. This may occur for a number of reasons—from incomplete or incorrect data entry to steps put in place by the health plan to require patients to "step" through other therapies in order to receive the prescribed medication. If the PA is not approved, however, an appeals process starts. The case manager will follow up with the health plan once the physician office completes the appeal and resubmits for authorization. Some pharmaceutical companies have field-based individuals who are able, if requested, to support the physician office through the appeals process by securing the correct payer-specific and/or drug class or disease-specific forms. The appeal process can cause significant delays and may involve first or second appeal and/or a

peer-to-peer physician conversation between a health plan physician and the prescriber. The physician office has the ultimate responsibility for getting these medications approved. If the appeal is not successful and coverage is denied, the physician may prescribe an alternative medication, or the hub/specialty pharmacy case manager may work directly with the patient to offer financial assistance for short term or long term, as required.

Health Plan

PAH drugs are costly, and health plans implement measures designed to ensure that the "right patient gets the right drug at the right time." Patients and providers may see these measures, such as PAs and step-edits, as roadblocks. Health plans have written medical policies based on evolving medical science and evidence-based clinical guidelines to assist in administering health benefits. These policies are usually reviewed annually and are intended to be used along with medical judgment in making clinical decisions for their patient populations. It is important that health plans have open access to all the PAH medications because patients may respond differently to a single medication. As the disease progresses, functional status that is lost may not be regained (EARLY,[7] AMBITION[8]).

Specialty Pharmacy

Health plans use Specialty Pharmacies (SPs) to dispense PAH medications. The patient's enrollment is next pushed out to the SP that will distribute the medication. The SP adjudicates coverage and provides the patient with more detailed information about their coverage. Once again, if the patient cannot afford the medication, the hub case manager gets involved to assist the SP with financial coverage options for the patient. The SP collaborates with the physician's office to obtain approval from the health plan and to coordinate delivery of the medication to the patient.

The SP also offers services such as nursing support, education, monitoring, and adherence programs. Nursing education may be required before the start of therapy, in the home or the health care facility, and may continue for some time, as in the cases of titratable PAH therapies. For example, with selexipag and riociguat, the physician has the option to order from one to several nursing visits, based on patient need. Communication between SP pharmacists and the patient continues throughout the time the patient is on PAH medications. Monthly calls to assess the patient's well being and any side effects occur before reordering of medication, and in most cases, a 24-hour hotline is available to the patient for emergencies. Good communication between the SP, the physician office, and the patient enables smooth initiation and continued safe use of the prescribed PAH therapy.

Conclusion: The Successful "Village"

With a rare disease like PAH and the costly therapies used to treat it, it is imperative that the medications are prescribed and used in appropriate patient populations. The patient benefits from the collaboration of all the players involved in PAH patient care. This complex disease process requires a dedicated network—or village—to provide ongoing education, access to medications, and support throughout the disease process.

Patients must receive their medications, both initial and refills, in a timely manner, and must be educated and supported throughout therapy to facilitate adherence with their treatment regimen. When patients know that they are not alone, they are better able to navigate through the health system, make better use of resources, and gain more control over their disease and their lives. ■

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Questions

1. In pulmonary arterial hypertension (PAH), there is proliferation of the endothelium of the pulmonary arterioles and smooth muscle cell hypertrophy with narrowing of the vessel lumen.
   a. True
   b. False

2. PAH leads to:
   a. Increased pulmonary vascular resistance
   b. Right ventricular remodeling
   c. Right ventricular dysfunction
   d. All of the above

3. What is the average life expectancy after a diagnosis of PAH?
   a. 3 years
   b. 5 years
   c. 7 years
   d. 9 years

4. A key to treatment of PAH is timely access to treatment medications.
   a. True
   b. False

5. Patient-centered care primarily focuses on the treating team.
   a. True
   b. False

6. Numerous resources exist for the patient with PAH, including:
   a. Professionals in centers/clinics
   b. Specialty pharmacies
   c. Pulmonary Hypertension Association
   d. All of the above

7. Pharmacologic treatment takes into consideration:
   a. Stage of the disease
   b. Comorbidities
   c. Support systems
   d. All of the above

8. The PAH treating team provides:
   a. Education about the disease
   b. Treatment goals
   c. Therapies
   d. All of the above

9. The "hub" provided by the PAH medication manufacturer provides the following services:
   a. Benefit verification
   b. Assistance with the prior authorization
   c. Education and information
   d. All of the above

10. Because of the complex disease process of PAH and its costly therapies, a dedicated network/team is required to provide ongoing education, access to medications, and support throughout the disease process.
    a. True
    b. False

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Objectives

March 2018

1. Define pulmonary arterial hypertension.
2. Define the patient and provider team.
3. State four players in accessing PAH medication.

Answers

Please indicate your answer by filling in in the letter:

1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____ 7. _____ 8. _____ 9. _____ 10. _____

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