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Pulmonary Arterial Hypertension: Classification and Therapy With a Focus on Prostaglandin Analogs

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Pulmonary arterial hypertension, part of the larger spectrum of disorders causing pulmonary hypertension, is a complex and progressive disease of multiple etiologies that ultimately leads to vascular remodeling, right-sided heart failure, and death. Advances in treatment over the past 15 to 20 years have dramatically reduced the morbidity and mortality of the disease, but often have significant drawbacks. Of the more recently approved therapies, the prostaglandin analogs have been shown to have the greatest therapeutic benefit but are also the most difficult to administer, many being given as continuous intravenous infusions in the ambulatory setting. After a case presentation highlighting some of the challenges that accompany treatment with these agents, this article reviews the diagnosis and classification of pulmonary hypertension and pulmonary arterial hypertension and gives a brief overview of the various other pharmacologic agents used in its treatment. A more comprehensive review of the biochemistry of prostaglandins and the pharmacology and clinical use of this class of drugs follows. Recommended treatment guidelines are also discussed.

Keywords: pulmonary hypertension, pulmonary arterial hypertension, prostaglandins, epoprostenol, treprostinil, iloprost

CASE REPORT

A 46-year-old woman with primary sclerosing cholangitis and autoimmune hepatitis underwent liver transplantation in 1999. She had recurrence of her liver disease diagnosed in 2004 and was eventually listed for a liver retransplant. Portopulmonary hypertension was subsequently diagnosed in 2009. She was World Health Organization Functional Class II, but her hemodynamic parameters, specifically her mean pulmonary artery pressure of 57 mmHg, caused her to be temporarily taken off of the liver transplant list. After a trial of sildenafil (Revatio, Pfizer, New York, NY) monotherapy, she was eventually placed on a therapeutic regimen of oral tadalafil (Adcirca, Eli Lilly and Company, Indianapolis, IN) and the prostaglandin analog treprostinil (Remodulin, United Therapeutics Corp., Research Triangle Park, NC) administered through a continuous ambulatory infusion pump. As a result of the risk of hemodynamic collapse, the infusion was initiated per protocol under close monitoring in the medical intensive care unit. After an uneventful hospitalization and discharge, the dose of treprostinil was being titrated up on an outpatient

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basis with improvement in her symptoms to World Health Organization functional Class I.

However, before reaching the target dose, she was admitted to the hospital for cellulitis of the left lower extremity approximately 2 months after the infusion was started. Three days after admission, she developed Gram-negative sepsis and became hypotensive. Before transfer to the medical intensive care unit, the treprostinil infusion was interrupted for approximately 4 hours. As a result, widespread pulmonary vasoconstriction developed, which led to acute right heart strain and near cardiogenic shock with a significant decrease in cardiac output, exacerbating her septic shock.

The patient's hemodynamics ultimately stabilized with appropriate therapy for her septic shock. An infusion of a different prostaglandin agent, epoprostenol (Flolan, GlaxoSmithKline, Research Triangle Park, NC), was substituted for treprostinil out of concern for possible immunosuppressant effects of the latter. However, as a result of this chain of events, her liver function began to decline at a more rapid pace. She also developed renal failure and was ultimately listed for combined hepatic–renal transplant after bedside hemodynamic monitoring revealed that the epoprostenol therapy had reduced her mean pulmonary artery pressure below the threshold to qualify for relisting. This double transplant was successfully performed almost exactly 1 month after the septic episode.

The epoprostenol infusion was continued, and after a relatively uneventful postoperative course, the patient was discharged with a follow-up clinic visit 4 weeks later. At present, the dose is being weaned down on an outpatient basis until the infusion can ultimately be discontinued completely. Serial measurements of N-terminal pro-B-type natriuretic peptide (NT proBNP) has shown declining values despite weaning epoprostenol, indicating improving cardiac function.

OVERVIEW OF PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is a heterogeneous group of disorders with the common definition of a mean pulmonary artery (PA) pressure 25 mmHg or greater or systolic PA pressure 40 mmHg or greater. PH is further separated into five subtypes. Group I, pulmonary arterial hypertension (PAH) is further defined as having a pulmonary capillary wedge pressure of 15 mmHg or less with none of the coexisting etiologies that lead to Group II through V PH. Group I is the only type of PH that will be further discussed here and includes idiopathic pulmonary arterial hypertension (IPAH), previously termed primary pulmonary hypertension, as well as many other causes, including the example used in the case presentation, portopulmonary hypertension. Other notable examples of PAH include PH associated with connective tissue diseases (eg, systemic sclerosis or scleroderma), congenital heart disease, and the use of drugs such as the anorectic agent fenfluramine.[1] The remaining classes of PH are summarized in Table 1.[1] Disease severity and prognosis are based only in part on certain hemodynamic parameters such as mean right atrial pressure and cardiac output. Treatment decisions, however, are driven primarily by New York Heart Association/World Health Organization functional class[2,3] and not PA pressure, as discussed subsequently. Functional class is summarized in Table 2;[4] both it and the 6-minute walk distance (6MW) are commonly used as indicators of response to therapy and are considered by most investigators to be key prognostic factors, perhaps more so than hemodynamic variables, because they are both independently associated with mortality Importantly, they are easily measured clinically without the need for invasive testing.[5–8] The 6MW is used as the primary end point in the vast majority of the clinical trials that are discussed subsequently with improvement in functional class as a secondary end point. Serum markers have also shown to be clinically useful: BNP and NT proBNP, for example, have data to support their use both prognostically and to monitor response to therapy. A decline from baseline values indicates a favorable response to therapy and, consequently, a better prognosis.[9,10]

TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

Treatment of PAH consists of both "conventional agents" and more recently developed or "advanced therapies" approved specifically to treat this disease. Conventional agents include calcium channel blockers (CCBs), anticoagulation (generally with warfarin), diuretics, digoxin, and supplemental oxygen. To date, the newer pharmaceutical agents approved for the treatment of PAH fall into three therapeutic classes: endothelin receptor antagonists, phosphodiesterase 5 (PDE5) inhibitors, and prostaglandin analogs.[2,3] The prostaglandin analogs are the only agents not currently available in the United States as an oral formulation and is the major focus of this review.

CONVENTIONAL AGENTS

None of the agents in this category have any randomized controlled trial (RCT) data to support their use.

Table 1. Updated clinical classification of pulmonary hypertension (dana point, 2008).[1]

Group 1: Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. Heritable PAH
1.3. Drug- and toxin-induced PAH
1.4. PAH associated with other diseases
1.4.1 Connective tissue disease
1.4.2. HIV
1.4.3. Portal hypertension (portopulmonary hypertension)
1.4.4. Congenital heart disease
1.4.5. Schistosomiasis
1.4.6. Chronic hemolytic anemia
1.5 Persistent pulmonary hypertension of the newborn
Group 1′: Pulmonary Veno-occlusive disease (VOD) and/or pulmonary capillary hemangiomatosis
Group 2: Pulmonary hypertension owing to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
Group 3: Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease (COPD)
3.2. Interstitial lung disease
3.3. Other lung diseases with a mixed obstructive/restrictive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)
Group 5: Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematologic disorders (myeloproliferative disorders, postsplenectomy)
5.2. Systemic disorders (sarcoid, pulmonary Langerhans cell histicytosis)
5.3. Metabolic disorders (glycogen storage diseases, Gaucher disease, thyroid disease)
5.4. Others (chronic renal failure, fibrosing mediastinitis)

Table 2. World health organization functional class in pulmonary hypertension (PH).[10]

Class I: PH but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or near syncope
Class II. PH resulting in slight limitation of physical activity. Comfortable at rest but ordinary physical activity results in undue fatigue or dyspnea, chest pain, or near syncope
Class III. PH resulting in marked limitation of physical activity. Comfortable at rest but less than ordinary physical activity causes undue fatigue or dyspnea, chest pain, or near syncope
Class IV. PH resulting in inability to carry out any physical activity without symptoms. Patients manifest signs of right heart failure. Dyspnea and/or fatigue are present even at rest. Discomfort is increased by any physical activity

Note: The WHO functional classification system for PH is based on the New York Heart Association functional classification for heart failure and is therefore virtually identical. The names are often used interchangeably.

Anticoagulation was shown to have a survival benefit in three retrospective studies.[11–13] A later trial evaluating the use of CCBs also demonstrated that anticoagulation was associated with better survival.[14] Diuretics are used for sequelae of right heart failure, where they have an obvious role.[3] There are no long-term data on the use of digoxin; it has only been shown to have short-term benefits by reducing catecholamine levels and increasing cardiac output in patients with right heart failure when given intravenously.[15] CCBs have the most robust data on long-term survival benefit but only in a select group of patients, as described subsequently.

Other agents with vasodilatory actions such as hydralazine and angiotensin-converting enzyme inhibitors were previously evaluated as potential therapies for PAH in uncontrolled trials or case series.[16–19] These therapies were shown to have mixed or negative results and have since been largely abandoned in favor of CCBs. There is currently no established role for them in PAH.[2,3] Although there are emerging data about a possible role of agents that affect angiotensin-converting enzyme Type 2, this has only been investigated in animal models.[20,21]

Calcium channel blockers

CCBs were the earliest drugs available to have shown a long-term survival benefit in PAH, albeit only in a select group of patients (26%) who responded to the therapy.[14] A more recent study by Sitbon et al[22] defined responders to CCB therapy as those who demonstrate a reduction in mean PA pressure by 10 mmHg or greater to reach a mean PA pressure of 40 mmHg or less with an normalized or increased cardiac output with an acute vasodilator challenge (eg, inhaled nitric oxide) during right heart catheterization. Less than 10% of patients in their cohort showed long-term benefit with even some patients having a positive vasoreactivity test failing to maintain a long-term response to CCB therapy. In a much smaller series of 16 patients, the rate of response to CCBs was noted also to be less than 10%.[23] In both the 1992 and 2005 studies, 5-year survival in responders was in excess of 90%, whereas that of nonresponders was less than 50%.

The specific agents that have consistently demonstrated efficacy are diltiazem (60–120 mg three times a day) and nifedipine (10–20 mg three times a day)[14,24] titrating upward to the highest dose that does not cause significant bradycardia or hypotension. There are limited data on the use of amlodipine[22,25] as well. It is important to realize that by virtue of their negative inotropic properties, CCBs are known to have deleterious hemodynamic effects such as acute systemic hypotension or decreased cardiac output[24,26] in nonresponders; this has been postulated to be attributed either to chronic changes in the pulmonary vasculature or right heart chambers from advanced disease[24] versus possibly representing a separate disease process.[22] Therefore, empiric therapy with these agents is contraindicated and all patients should be tested for vasoreactivity before this therapy is started.[3,22]

ADVANCED THERAPIES

Endothelin receptor antagonists

Bosentan (Tracleer, Actelion Pharmaceuticals US Inc., South San Francisco, CA) was approved by the Food and Drug Administration for treatment of PAH in 2001. Ambrisentan (Letairis, Gilead Sciences, Inc., Foster City, CA) was approved under orphan drug status in 2007. A third agent, sitaxsentan (Thelin, Pfizer), had been approved in the European Union, Canada, and Australia. However, after cases of fatal hepatotoxicity occurred during Phase III trials in the United States, it was voluntarily pulled from the market worldwide by the manufacturer in December 2010.

These agents act by blocking the endothelin-1 (ET-1) receptors. There are two major receptor types, Type A (ET_A) and B (ET_B). In the pulmonary vascular bed, ET_A receptors are found primarily in smooth muscle, whereas ET_B receptors are found in both smooth muscle and endothelial cells. Stimulation of both types of receptors in smooth muscle cells results in potent vasoconstriction[27] and mitogenic effects.[28,29] ET_B receptors on endothelial cells, however, have been shown (primarily in animal models) to mediate some potentially beneficial effects in PAH, including increased clearance of ET-1[30] and stimulation of the release of the vasodilatory agents nitric oxide and prostacyclin.[31] The data are inconclusive as to whether selective antagonism is more effective, likely as a result of compensatory mechanisms that become active when ET_A alone is blocked.[29] A single comparative study has been performed in rats: although there was a survival trend favoring nonselective antagonism, the hemodynamic data were similar; thus, the authors did not feel that it was conclusive.[32] Of the two available agents in this class, ambrisentan selectively antagonizes ET_A receptors, whereas bosentan is nonselective.

Bosentan (Tracleer)

Bosentan is a nonselective endothelin receptor antagonist. It was shown in the BREATHE-1 (Bosentan Randomized trial of Endothelin Antagonist THErapy for pulmonary hypertension) trial to improve hemodynamic parameters, 6MW, and World Health Organization functional class, in a statistically significant manner, compared with placebo. Forty-two percent of patients improved by at least one functional class at 16 weeks (compared with 30% with placebo).[33] Later studies also demonstrated a survival benefit: McLaughlin et al demonstrated 89% survival at 24 months compared with 57% in historical controls.[34] A second study, examining 103 consecutive patients in France with functional Class III or IV disease, also showed 89% percent survival at 24 months.[35] However, a significant proportion (24% and 44%, respectively) of the patients started on bosentan as first-line therapy in these studies could not be maintained on monotherapy alone. This generally meant addition of ''prostanoid therapy'' in patients with worsening (or no improvement in) functional Class III or IV disease.

Bosentan is given orally twice daily at a starting dose of 62.5 mg for 4 weeks and then increased to 125 mg twice daily. There are no data to suggest significant potential for rebound worsening of disease, but should it need to be discontinued, it is recommended that the dose be tapered back down to 62.5 mg for several days before doing so. The major adverse reactions are hepatotoxicity (transaminase elevations greater than three times the upper limit of normal) and teratogenicity (Category X). There are drug–drug interactions with two other commonly used drugs in PAH, warfarin and sildenafil. In both cases, plasma concentrations of the other drugs were decreased. Sildenafil also increases plasma levels of bosentan. However, no dose adjustment has been recommended.[36]

Ambrisentan (Letairis)

Ambrisentan is a selective endothelin receptor Type A antagonist. An open-label initial trial by Galié et al showed similar results to those mentioned for bosentan, increasing 6MW distance, and functional class also improved in 36% of patients.[37] The later ARIES-1 and ARIES-2 trials (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies) were concurrent double-blind placebo-controlled RCTs evaluating the efficacy of ambrisentan. Although 6MW distance

increased in statistically significant amounts compared with placebo in both trials, functional class did not similarly improve in ARIES-2. Functional class did improve in ARIES-1, however, and the effect seen in ARIES-1 was large enough to make the combined data reach significance as well.[38]

Ambrisentan appears to have a lower incidence of transaminase elevations compared with the other endothelin receptor antagonists and has been shown to be effective as an alternate agent in patients who had to discontinue bosentan or sitaxsentan as a result of such hepatic effects.[39]

Ambrisentan is given as a single daily oral dose, starting at 5 mg and increasing to 10 mg if tolerated. Similar to bosentan, it is also pregnancy Class X and is not thought to change plasma levels of other PAH drugs (ie, sildenafil) in a clinically significant fashion.[40]

Phosphodiesterase 5 inhibitors

Two PDE5 inhibitors, sildenafil (Revatio; Viagra, Pfizer) and tadalafil (Adcirca; Cialis, Eli Lilly and Company), have been approved by the Food and Drug Administration for the treatment of PAH. Sildenafil was the first agent approved in 2005. PDE5 is the predominant enzyme for the metabolism of cGMP in the lung. Inhibition of PDE5, therefore, increases intracellular levels of cGMP, enhancing nitric oxide-mediated vasodilatation in the pulmonary vasculature.[41] There may also be some antiproliferative effects on vascular smooth muscle as well.[42]

Sildenafil (Revatio)

Sildenafil was shown in a multicenter, double-blind RCT to improve 6MW, functional class, and hemodynamics in patients with PAH at 12 weeks of treatment. It did not reduce time to clinical worsening compared with placebo. The study was not powered to assess mortality, but the other benefits were maintained at 1 year.[43] Unfortunately, the only long-term data available on sildenafil involved doses higher than the Food and Drug Administration-approved dose of 20 mg three times a day.[43,44] The subsequent Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil (PACES) trial, in which sildenafil (80 mg three times a day) or placebo was added to background eporostenol, also showed significant benefit in 6MW, hemodynamics, and quality of life in the sildenafil group. There was also improvement in time to clinical worsening, unlike the earlier study.[45]

Tadalafil (Adcirca)

Tadalafil was approved only recently for treatment of PAH. The Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST-1) study demonstrated statistically significant improvement in 6MW in both treatment-naïve and patients already on bosentan. There was no significant improvement in functional class, but there was a decrease in time to clinical worsening. There was a somewhat blunted response to treatment in the patients already on bosentan, leading the authors to hypothesize that the pharmacokinetic interaction between the two agents that decreases the effect of tadalafil is responsible, similar to that seen with sildenafil. Another possibility is that there is a ceiling phenomenon that limits the response as additional therapies are added.[46] Data from the long-term extension of that trial have not yet been published. As in the case of sildenafil, there are no data showing a statistically significant mortality benefit.[47] Tadalafil's comparatively long half-life gives it the advantage of once-daily dosing at a dose of 40 mg.

PROSTAGLANDIN ANALOGS

The prostaglandin analogs are the preferred first-line treatment for World Health Organization Functional Class IV PAH. There are three agents in this class currently approved by the Food and Drug Administration for treatment of PAH: epoprostenol, iloprost, and treprostinil. A fourth, beraprost, is the only oral agent in the class that has received regulatory approval. It is approved for use in Southeast Asia and is currently undergoing Phase II trials in the United States.[48] Oral treprostinil is also currently in clinical trials. Epoprostenol is a synthetic form of prostacyclin. The remaining agents are considered prostaglandin analogs. The chemical structure of these molecules is shown in Figure 1.

BIOCHEMISTRY OF PROSTANOIDS

The naturally occurring prostanoids are metabolites of arachadonic acid pathway[49] that are divided into two major groups: prostaglandins and thromboxanes. Together, these two groups of mediators are called prostanoids. The term prostanoid is often incorrectly applied to synthetic analogs of prostaglandins. Cyclooxygenase-1 and -2 convert arachidonic acid into a common precursor, which is then acted on by individual prostaglandin synthases to form the final metabolically active compounds, as shown in Figure 2.[50] There are five principal prostanoids, thromboxane A_2, prostaglandin D, E (PGE), F, and I (PGI). Prostacyclin, the molecule on which epoprostenol and the other agents in the class are based, is PGI.

Further nomenclature places a subscript indicating the number of double bonds on the side chains attached to the main cyclopentane or cyclohexane ring

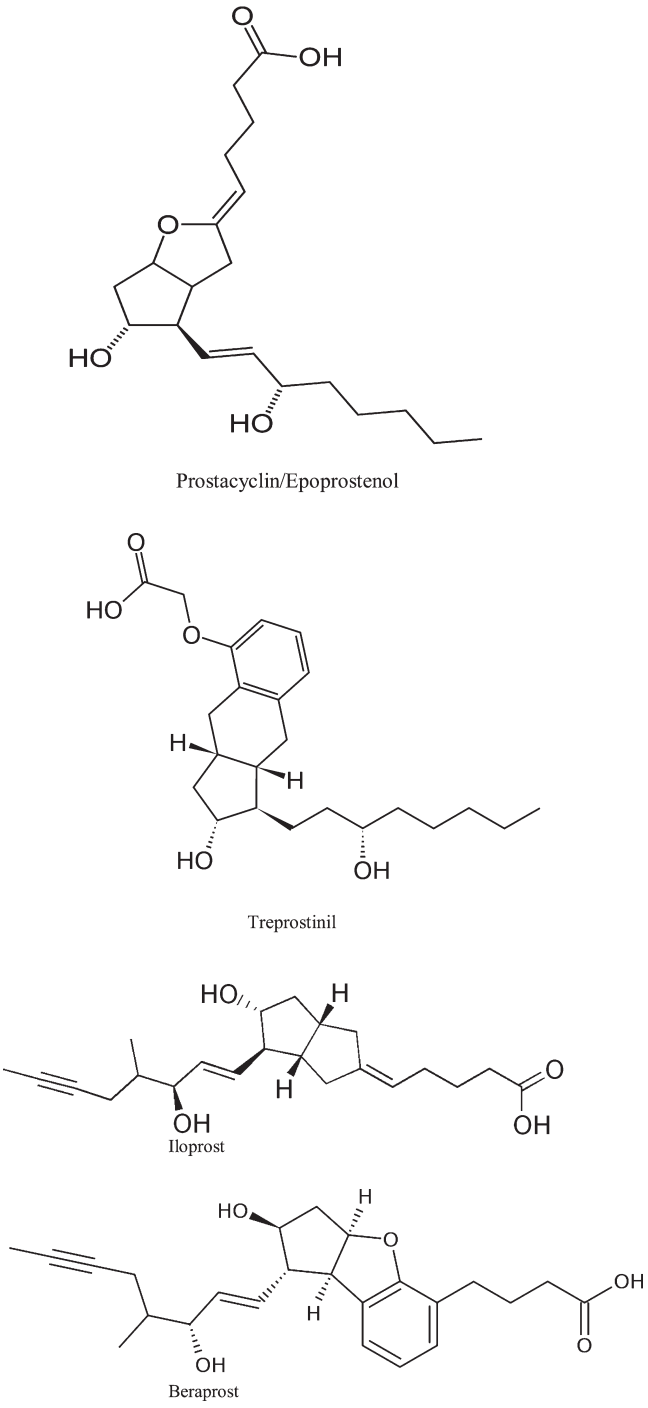

FIGURE 1. Chemical structures of the major prostaglandin analogs.

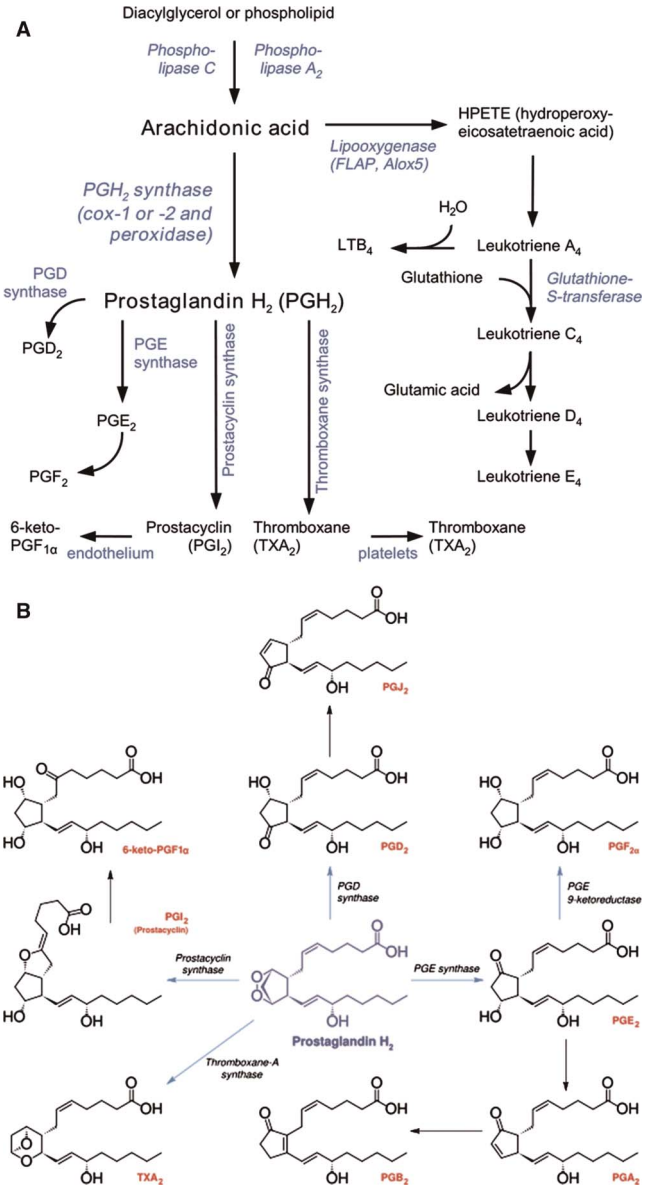

FIGURE 2. (A) Arachidonic acid metabolism. (B) Prostaglandin synthetic pathways.

(eg, PGE_2). Table 3 summarizes the major physiological roles of various prostaglandins.[50-56]

The known prostanoid receptors and their respective G-protein-coupled receptors, along with their actions on second-messengers (primarily cyclic adenosine monophosphate [cAMP]) are listed in Table 4.[57,58]

The receptors are named for the prostanoid (prostaglandin or thromboxane) that binds most readily to them. It is not known how much cross-binding affinity the receptors possess for other prostanoids.

The prostanoid receptors can be grouped into two categories based on the G-protein they activate and the consequent cellular response.[49,51] The first category consists of relaxant receptors, which generally act through the G-protein G_s, which increases the production of cAMP in the target cells. The receptors in this category are IP, EP_2, EP_4, and DP. The second category, contractile receptors, consists of TP, EP_1, and FP. These

Table 3. Examples of the major physiological roles of prostaglandins by organ system.[50–56]

Organ system	Prostaglandin	Synthetic cell or site	Primary effect
Cardiovascular	Prostacyclin (PGI_2)	Endothelium	Vasodilatation
Gastrointestinal	PGE_2	Gastric/colonic mucosa	Cytoprotective
Hematologic	PGI_2	Endothelium	Deaggregation of platelets
Musculoskeletal	PGE_2	Osteoclasts	Bone remodeling
Renal	PGI_2	Cortex	Vasodilatation
	PGE_2	Medulla	Salt/water excretion
Reproductive	PGE_2	Seminal vesicles	Erection, ejaculation, sperm transport
	PGE_2, PGF_2	Fetal membranes	Parturition/labor
		Uterus	Ovulation, fertilization, menstruation
Respiratory	PGI_2	Endothelium	Vasodilatation
	PGD_2	Bronchial epithelium	Bronchoconstriction
Neurologic	PGE_2	Not known	Fever, nociception/hyperalgesia

activate G_q, which ultimately increase intracellular calcium levels through the second messenger phosphatidylinositol. Note that the specific G-protein activated by a certain prostanoid receptor will differ between cell types and can be influenced by the concentration of the ligand. For example, IP generally activates G_s but will activate G_q if it is present in high enough concentrations.

PROSTAGLANDINS OTHER THAN PGI

Prostaglandin D is associated with the DP receptor. It is the major prostaglandin produced by activated mast cells and has a role in both IgE-mediated Type I hypersensitivity reactions[59] as well as being implicated in various pathologic processes in asthma, including airway remodeling and bronchoconstriction.[50]

Prostaglandin E (PGE_2), of all the prostaglandins, is produced in a wide variety of tissues and has a similarly wide range of actions, having both pro- and anti-inflammatory effects depending on the cell and receptor types involved.[50] It can act on vascular smooth muscle to cause both vasoconstriction or vasodilatation in various organ beds.[60,61] This is well illustrated in Table 3 and can be explained in part by the existence of four EP subtypes, $EP_{1–4.}$ Each subtype, in turn, can have differing effects depending on the G-protein-coupled receptor they act on at the intracellular level (Table 4) or the specific cell they interact with. For example, EP_4 receptors play a role in closure of the ductus arteriosus, facilitate the differentiation of osteoclasts from precursor cells,[53] and can play a protective role in inflammatory bowel disease[52] but have been implicated in the pathogenesis of colon cancer.[54] PGE_2 is well known to be involved in nociception and thermoregulation; multiple EP receptor subtypes have been implicated.[49,51]

In the lung, EP_2 receptors have vasodilatory actions through the G_s protein, which increases intracellular cAMP. In this instance, the elevated cAMP levels hyperpolarize the cell membrane of smooth muscle cells by opening calcium-activated potassium channels.[62–64]

Table 4. Prostanoid receptors and their associated G-protein-coupled second messenger activity.[57,58]

	Specific receptor	Associated G-protein	Second messenger effect
DP receptors	DP	G_s	Increases cAMP
EP receptors	EP_1	Unknown	Increases intracellular Ca^{2+}
	EP_2	G_s	Increases cAMP
	EP_{3A}	G_i	Decreases cAMP
	EP_{3B},EP_{3C}	G_s	Increases cAMP
	EP_{3D}	G_i	Decreases cAMP
		G_s	Increases cAMP
		G_q	Increases turnover of phosphatidylinositol (PI)
	EP_4	G_s	Increases cAMP
FP receptors	FP	G_q	Increases cAMP or PI turnover
IP receptors	IP	G_s,G_q	Increases cAMP or PI turnover

EP_3 receptors, in contrast, produce vasoconstriction of the pulmonary vascular bed. They do so through both G_q and G_i proteins. G_i-linked EP_3 receptors decrease cAMP levels, whereas G_q-linked receptors increase intracellular calcium levels through phosphatidylinositol metabolism.[57]

Pharmaceutical agents that act on EP receptors include misoprostol (Cytotec, G.D. Searle, LLC, New York, NY), which is commonly used for the prevention of peptic ulcers related to nonsteroidal anti-inflammatory drug use, and as an adjunct for cervical ripening in childbirth as well. Alprostadil is used under the brand name Caverject (Pharmacia and Upjohn Co., Kalamazoo, MI) for the treatment of erectile dysfunction and is also used for treatment of patent ductus arteriosus.

Prostaglandin F_2 has a number of known functions, including a role in menstruation,[65,66] and cardiac hypertrophy.[67] FP receptors have been widely used as a therapeutic target in glaucoma; travoprost (Travatan), latanoprost (Xalatan), and bimatoprost (Lumigan) are all prostaglandin F_2 agonists approved by the Food and Drug Administration for the treatment of glaucoma and ocular hypertension. The FP receptor is relatively nonselective, readily binding both prostaglandin D_2 and PGE_2.[68]

Prostacyclin (prostaglandin I, PGI_2)

Prostacyclin, as stated previously, is the molecule on which epoprostenol and the other agents in its class are based. Endogenously, it is produced by vascular endothelium[69] and inhibits the proliferation, differentiation, and migration of vascular smooth muscle cells. It also causes relaxation of these cells. In addition, prostacyclin inhibits platelet aggregation and plays a role in hemostasis.[70] In ischemia–reperfusion injury, it has been shown to have a cardioprotective effect.[71] Like with other prostaglandins, PGI_2 is a mediator of inflammation and nociception.[72,73]

The IP receptor primarily couples with the G_s protein and increases the intracellular concentration of cAMP in much the same way as EP_2 receptors.[62–64] Unlike EP_2, however, which is expressed primarily in the pulmonary veins,[74] the IP receptor is present on both the arterial and venous sides of the pulmonary bed, [64] which could explain the effectiveness of prostacyclin and its analogs compared with that of the other prostaglandins in PAH. [48]

INDIVIDUAL PROSTACYCLIN ANALOGS

Epoprostenol (Flolan, Veletri)

Epoprostenol, as noted previously, is a synthetic form of prostacyclin and was approved in 1995 as the first agent in the class. The Food and Drug Administration has approved epoprostenol for New York Heart Association/World Health Organization functional Class III or IV IPAH or PAH associated with systemic sclerosis/scleroderma. It is administered by continuous intravenous infusion. Like with all of the drugs in this class, it is recommended that it only be prescribed by a clinician experienced in the diagnosis and treatment of PAH.

One of the pivotal trials in its approval was a multicenter, open RCT comparing epoprostenol plus conventional therapy to conventional therapy alone in patients with Class III or IV IPAH (known at the time as primary pulmonary hypertension). At 12 weeks, 6MW, quality-of-life measurements, and hemodynamic variables all improved in the 40 patients in the epoprostenol group but declined in the 40 patients in the control group (P values of < 0.002, < 0.01, and < 0.001, respectively). Additionally, a survival benefit was established, because eight patients in the control group died during the study, whereas no patients in the epoprostenol group did ($P = 0.003$).[8] An earlier study by the same group also demonstrated a survival benefit compared with historical controls[75] as did a later nonrandomized series of over 100 consecutive patients seen at a single center.[76]

Another trial looked at 111 patients with PAH associated with scleroderma. In this open-label RCT, there was statistically significant improvement in functional class and 6MW at 12 weeks, but there was no survival benefit compared with conventional therapy.[77]

Epoprostenol binds primarily to the IP receptor. It has a very short half-life of 3 to 5 minutes and is unstable at physiological pH (less than 10.5). It therefore needs to be administered by continuous infusion.[78] It is so unstable, in fact, that the pharmacokinetics are poorly characterized.

Furthermore, the standard preparation (Flolan) must remain refrigerated in a glycine buffer solution during administration and needs to be freshly prepared from its freeze-dried storage form with the buffer solution every 24 hours as a result of its instability. A newer preparation, marketed under the trade name Veletri (Actelion Pharmaceuticals US, Inc.), does not require refrigeration and can be mixed with sterile water or 0.9% saline. In both cases, an ambulatory infusion pump meeting certain specifications is used to administer the drug through an indwelling central venous catheter.[79,80]

Long-term dose titration of epoprostenol is necessary to overcome tachyphylaxis. The IP receptor is thought to undergo not only agonist-induced desensitization,[81] but also an independent process of agonist-induced receptor sequestration and internalization.[82] Typically, a patient will require uptitration of the dose over a period of 6 months to a level of 20 to 40 ng/kg/min.

The common or notable side effects of epoprostenol therapy (unrelated to the delivery system) are headache, jaw or chest pain, nausea, and flushing. Adverse events related to the delivery system include catheter-related thrombosis, hemorrhage, infection (bloodstream or insertion site), and pneumothorax.[8,76] In addition, there is evidence to support immunosuppressive effects of the drugs in this class, which are discussed separately subsequently in a later section devoted to reactions common to all drugs in the class.

Treprostinil (Remodulin, Tyvaso)

Treprostinil is a prostaglandin analog first approved by the Food and Drug Administration for treatment of Class II to IV PAH (all subtypes of PAH) as a subcutaneous infusion (Remodulin) in 2002. The majority of the data to support its use are for this route of administration. It was later approved in the same formulation for intravenous use through bioequivalence. It has been shown to be effective in IPAH, PAH associated with collagen vascular diseases, and PAH resulting from congenital left to right shunts.

A 12-week multicenter, placebo-controlled RCT with this mixed patient population demonstrated statistically significant improvement in 6MW (the primary end point), quality-of-life indices, and hemodynamics compared with placebo. Infusion site pain and equipment malfunctions were very common.[83]

Later studies have looked at transitioning from long-term epoprostenol to either subcutaneous or intravenous treprostinil. It has been shown in both adult and pediatric populations that the transition can be made successfully both over short- (24–48 hours) and long- (up to 14 days) intervals.[84–87] Side effects are reportedly less than that seen with epoprostenol, and long-term safety data on treprostinil show similar results to the earlier 12-week trials.[88]

Inhaled treprostinil (Tyvaso, United Therapeutics Corp.) was studied in the Phase III Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension (TRIUMPH-1) trial, reported recently.[89] This trial looked at 235 patients with PAH already on oral therapy (bosentan or sildenafil). There was statistically significant improvement in 6MW and quality of life as well as NT proBNP levels. There was no improvement in functional class compared with placebo.

Combination therapy with bosentan and subcutaneous treprostinil was retrospectively studied by Benza et al.[90] In this study, patients on treprostinil therapy were placed on bosentan as a second agent if they persisted in functional Class III or worse or if they were Class II with major dose-limiting side effects from prostacyclin-based therapy. The addition of bosentan resulted in significant improvement in hemodynamics, 6MW, and symptoms, but not in functional class. The incidence of adverse events was similar to that of the agents used alone.

Finally, Phase III trials of an oral formulation of treprostinil are underway. The FREEDOM-C trial reportedly failed to meet its primary endpoint, and the FREEDOM-M trial is ongoing.

Treprostinil binds to IP and EP_2 receptors.[91,92] Unlike epoprostenol, it is stable at room temperature and physiological pH. Its effective half-life is 10 minutes (intravenously) or 60 minutes (subcutaneously) and is bioequivalent with either route.[93]

Treprostinil is more stable than epoprostenol, and the individual syringes can be used for 48 to 72 hours depending on the concentration. No refrigeration or special solution is required. Typical dosing for continuous intravenous or subcutaneous infusion ranges from 50 to 100 ng/kg/min.[48] It should be started at 1 to 4 ng/kg/min and increased by 1 to 2 ng each week until the target dose. Inhaled dosing starts at 18 μg four times a day to a goal dose of 54 μg four times a day. It is given through a proprietary inhalation device.[94,95]

Side effects are similar to, but reported to be lower in incidence than, epoprostenol, except in the case of the subcutaneous route. The subcutaneous route has been reported to have up to 88% incidence of significant infusion site pain. This often (8% or more[83]) leads to discontinuation of the drug or switch to the intravenous route. Other adverse events related to the route of administration such as catheter infections are also similar to epoprostenol.[84–87]

Iloprost (Ventavis)

Iloprost is a carbacyclin analog of prostacyclin approved by the Food and Drug Administration in 2004 for the treatment of Class III or IV PAH (all subtypes of PAH). An intravenous formulation has been approved in New Zealand, but in the United States and most of the rest of the world, it is approved only in inhaled form for PAH, although it has been approved in the intravenous form for the treatment of thromboangiitis obliterans in Europe.

A pivotal trial leading to iloprost's approval was a prospective,12-week placebo-controlled RCT looking at 203 patients with either PAH or Group 4 PH, chronic thromboembolic pulmonary hypertension. The primary end point of 6MW improvement of 10% or more and at functional class improvement of at least one level in the absence of clinical deterioration was met at 12 weeks in all patients treated with inhaled iloprost. Hemodynamic variables, when measured after inhalation, were significantly improved as well.[96] Although the end point was met in the combined patient population, including the patients with chronic thromboembolic pulmonary hypertension, the Food and Drug Administration

declined to approve iloprost for chronic thromboembolic pulmonary hypertension, citing inadequate evidence of benefit in that subpopulation.[97]

Combination therapy with bosentan has also been studied. Two separate trials examined the addition of inhaled iloprost to oral bosentan. The first,[98] which was primarily a safety study, had secondary end points of 6MW, functional class, and hemodynamic improvement and all showed significantly better results with the addition of iloprost. There was also a statistically significant delay in time to clinical worsening. However, a second study,[99] in which patients on bosentan were also randomized to the addition of iloprost or placebo, was terminated early when an interim analysis failed to show a benefit.

An open-label RCT looking at 30 patients in a four-armed design, with patients receiving one of two doses of sildenafil (12.5 or 50 mg) with or without inhaled iloprost, was able to demonstrate greater short-term hemodynamic improvement with the combination compared with monotherapy.[100] This study looked only at the acute response to therapy over the course of only a few hours. In summary, the data showed the greatest hemodynamic improvement with iloprost plus the 50-mg dose of sildenafil, followed by iloprost plus 12.5 mg sildenafil, with iloprost alone showing the least improvement. They also showed that when used alone, the higher dose of sildenafil was more effective. The authors concluded that there was likely a synergistic effect between the two agents with sildenafil potentiating and prolonging the effect of iloprost.

Iloprost binds to IP and EP_1, EP_3, and EP_4 receptors.[58,101] It is administered through one of two proprietary nebulizer devices using single-dose ampules with each inhalation taking approximately 10 minutes. It is rapidly absorbed systemically and reaches peak levels shortly after the completion of the inhalation. The serum half-life has been measured at roughly 6.5 to 94 minutes, but the effective half-life (in terms of duration of effect) was over 20 minutes.[102] An in vitro study performed in rabbits[103] demonstrated the rapid development of tolerance, because the response to aerosolized iloprost leveled off after 3 to 3.5 hours.

Inhaled iloprost is started at a dose of 2.5 μg inhaled for the first dose. If this is well tolerated, it should be increased to 5 μg per inhalation and maintained at that dose. The major drawback to this route is that it requires frequent administration, because the recommended dosing is six to nine times per day.[97] Experience from the major trials discussed suggested that the average patient in that tightly controlled situation used it on average just over seven times a day, and 90% of patients never administered the medication at nighttime. On average, patients received a dose equivalent to an infusion of 0.37 ng/kg/min, lower than an effective intravenous dose. The authors concluded that inhaled therapy would reduce overall drug requirements.[96]

Specific adverse reactions associated with iloprost included syncope and bronchospasm. In the 2002 trial, there were eight syncopal events in the iloprost group compared with five in the placebo group, but the events in the iloprost group were more likely to be considered serious, including one that resulted in head trauma. The authors theorized that it may be the result of a loss of treatment effect resulting from the intermittent dosing schedule. They did, however, note that similar effects have been seen with bosentan, suggesting that both agents may somehow potentiate exercise-induced hypotension, because many of the events occurred with physical activity. Incidence of cough or bronchospasm was roughly similar to placebo.[96] However, caution should be exercised if prescribing inhaled iloprost to patients with reactive airways disease of any type or chronic obstructive pulmonary disease because it has not been studied in those populations.

Beraprost

Beraprost is in Phase II trials in the United States and is approved for use in Japan and South Korea. It is an oral prostaglandin analog with a half-life of 1 hour. One initial study demonstrated improvement in 6MW but not in functional class or hemodynamics at 12 weeks. The 6MW improvement was only seen in patients with IPAH and not other types of PAH.[104] A subsequent long-term study showed reduced disease progression and improved 6MW distance at 6 months, but the benefit did not persist, and there was no difference compared with placebo at 9 or 12 months.[105]

ADVERSE REACTIONS—GENERAL

Minor adverse reactions common to this class of agents are generally related to the actions of prostaglandins in the body. Infusion site and jaw or chest pain is fairly common in all drugs in the class. Infusion site pain is nearly universal with subcutaneous infusions. Flushing, diarrhea, and nausea are also frequent. Most of these effects decrease over time.

The major adverse events can be divided into two categories: drug reactions and events related to the route of administration. Major drug reactions include hypotension-induced syncope, especially exertional, and there is some evidence to suggest these drugs suppress the immune system (discussed subsequently).

Adverse events related to the delivery method include minor events such as bronchospasm in the case of

inhaled agents but also more serious events such as infections of the indwelling catheter and complications of line placement such as bleeding or pneumothorax. These are commonly seen in any therapy that requires long-term indwelling catheters and are not necessarily unique to this class, although the varied bacteriology of some infections may suggest otherwise.

PROSTAGLANDIN ANALOGS AND IMMUNOSUPPRESSION

A few case reports and case series, along with data from animal models, suggest that immunosuppression may result from use of the various prostaglandin analogs. They may also do so in different ways, owing to the specific receptor affinity of each agent. Epoprostenol has been associated with Gram-positive infections and, in particular, infections with micrococcus species.[106] Micrococcal infections are generally only seen in immunocompromomised hosts. These infections may be the result of deficient phagocytosis mediated by IP receptors.[107] Treprostinil, in contrast, has been associated with Gram-negative infections, as occurred in the case presentation at the beginning of this review. Treprostinil, in particular, has been demonstrated to inhibit phagocytosis, cytokine generation, and bacterial killing to a greater extent than the other agents in this class. This is thought to be mediated by the EP_2 receptor.[91] It has also been shown to inhibit human lymphocyte cultures in a manner similar to that seen with cyclosporine.[108] Reports of sepsis in relation to treatment with other prostaglandin analogs, namely misoprostol[109] and alprostadil,[110] which do not involve indwelling catheter use, further support this hypothesis.

ADVERSE REACTIONS RELATED TO DOSE TITRATION

In our case report, the patient experienced severe rebound pulmonary hypertension and right heart strain after the treprostinil infusion was interrupted. This rebound phenomenon can occur with intravenous, subcutaneous, or inhaled[111] therapy in a manner similar to that seen with nitric oxide and can lead to acute decompensated right heart failure and cardiogenic shock. For this reason, patients need to be extensively trained in the administration of the drug and is why all patients on these therapies need to have continuous access to a backup delivery device at all times. This requirement is built in to the Food and Drug Administration prescribing information on all these agents.

TREATMENT ALGORITHM

Guidelines on choice of therapy for PAH have been issued by both the American College of Chest Physicians and the American Heart Association. The treatment algorithm is shown in Figure 2.[2] Patients who have demonstrated reactivity on right heart catheterization should be placed on CCBs. Only a very small minority of patients (primarily those with IPAH) will be positive on vasoreactivity testing and even fewer can be maintained for a prolonged period on CCB monotherapy. For the majority of patients, the recommended approach to treatment is based on their World Health Organization functional class. The definitions of each functional class are summarized in Table 2. For functional Class II patients, the choice of therapy is either oral sildenafil (Level A recommendation) or treprostinil (Level C), intravenously or subcutaneously. Note that these guidelines predate approval of tadalafil and ambrisentan. Patients in Class III should be placed on sildenafil, bosentan, epoprostenol, or iloprost (all Level A recommendations) or treprostinil (Class B for subcutaneous route, Class C for intravenous). If Class III patients deteriorate or fail to improve on monotherapy, combination therapy is recommended with an agent from two of the three classes. Patients diagnosed in Class IV should be placed on prostaglandin analog therapy first-line as a result of their poor prognosis, and epoprostenol is the only agent with a Level A recommendation for these patients. Bosentan and iloprost are Level B recommendations, with sildenafil and treprostinil having Level C recommendations. Like with Class III disease, patients who either do not improve or deteriorate should be placed on combination therapy. Patients who fail combination therapy should be considered for surgical measures, either atrial septostomy or lung transplantation, if they are surgical candidates.

Adjunctive treatments such as supplemental oxygen, diuretics, and digoxin should be considered on a case-by-case basis based on expert recommendation and not empiric data. Anticoagulation with warfarin, however, has a Level B recommendation for patients with IPAH. It should be considered, again based only on expert opinion, for other types of PAH.

CONCLUSIONS

PAH remains a progressive and ultimately fatal disease for the majority of patients. Fortunately, great strides in treatment have been made in the last two decades, which have significantly increased survival rates. The use of such "advanced therapies," as the name implies,

is outside the purview of most physicians. Although PDE5 inhibitors are among the most commonly prescribed drugs in the United States (albeit for another indication), the other two classes are far less familiar to the average healthcare provider. Although the endothelin receptor antagonists are given orally and need only minimal dose titration, prostaglandin analogs, the most potent of the therapeutic classes, are particularly fraught with peril. The dosing and administration of these drugs is of a high level of complexity, requiring specialized equipment and frequent titration under close supervision. The risk of rapid decompensation and even death with abrupt discontinuation is virtually unique among therapies delivered on an outpatient basis for any condition. Clinicians inexperienced in the use of these agents can therefore potentially cause great harm to patients dependent on such medications.

It remains the recommendation of major advisory bodies that the care of patients with PAH be referred to experts and/or specialized centers well versed in the evaluation and treatment of this condition. Nonetheless, the general care of these patients will commonly fall to the primary care provider or other clinician, who likely does not have such specialized training or experience. For that reason, a familiarity with the unique properties and pitfalls of these drugs can be an important component of any practitioner's fund of knowledge.

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