REVIEW ARTICLE

DRUG THERAPY

# Treatment of Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension is a disease of the small pulmonary arteries that is characterized by vascular proliferation and remodeling.[1,2] It results in a progressive increase in pulmonary vascular resistance and, ultimately, right ventricular failure and death. A diagnosis of primary (or idiopathic) pulmonary hypertension is made when no known risk factor is identified.[3,4] The diagnostic classification of pulmonary arterial hypertension is described in Table 1.[3] Despite recent major improvements in symptomatic treatments, no current treatment cures this devastating condition.[1,2,5-9] However, during the past 20 years, treatment options for patients with the disease have evolved to help prolong their survival and improve their quality of life.

## PATHOPHYSIOLOGICAL FEATURES

It is unclear whether the various types of pulmonary arterial hypertension share a common pathogenesis.[10,11] Three factors are thought to cause the increased pulmonary vascular resistance that characterizes this disease: vasoconstriction, remodeling of the pulmonary vessel wall, and thrombosis in situ.[11] A substantial number of molecules have been implicated as putative candidates in the pathogenesis of pulmonary arterial hypertension.[10-28] Advances in our understanding of the molecular mechanisms involved in this disease suggest that endothelial dysfunction plays a key role.[2,17,27,28] Chronically impaired production of vasoactive mediators, such as nitric oxide and prostacyclin, along with prolonged overexpression of vasoconstrictors such as endothelin-1, not only affect vascular tone but also promote vascular remodeling. Thus, these substances represent logical pharmacologic targets (Fig. 1).[2,17,27,28]

## NATURAL HISTORY AND SURVIVAL

Before the development of recent therapeutic options, idiopathic pulmonary arterial hypertension was rapidly progressive and led to right heart failure and death. In the 1980s, it was reported that the median survival of patients was 2.8 years after diagnosis.[29] The first large prospective studies showed an actuarial survival rate of 68 to 77 percent, 40 to 56 percent, and 22 to 38 percent at one, three, and five years, respectively.[29,30] These studies also showed that a poor prognosis was associated with a history of right heart failure, New York Heart Association (NYHA) functional class III or IV (Table 2),[31] elevated right atrial pressure, decreased cardiac output, elevated pulmonary vascular resistance, or low mixed venous oxygen saturation.

The development of new drugs has led to several placebo-controlled trials in recent years.[32] The question of which end points are most relevant in such trials has been the topic of intense discussion. The normalization of measures of cardiovascular hemodynamics would be an ideal end point, if it were possible. However, hemodynamics in the resting state improve only marginally in most patients, even when their clinical response



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**Table 1. Diagnostic Classification of Pulmonary Hypertension.***

| |
|---|
| **Pulmonary arterial hypertension** |
| Idiopathic |
| Familial |
| Associated with |
| Collagen vascular disease |
| Congenital left-to-right shunt |
| Portal hypertension |
| Infection with human immunodeficiency virus |
| Drugs and toxins |
| Other conditions† |
| Associated with substantial venous or capillary involvement |
| Pulmonary veno-occlusive disease |
| Pulmonary capillary hemangiomatosis |
| Persistent pulmonary hypertension of the newborn |
| **Pulmonary hypertension with left heart disease** |
| Left-sided atrial or ventricular heart disease |
| Left-sided valvular heart disease |
| **Pulmonary hypertension associated with lung disease or hypoxemia or both** |
| Chronic obstructive pulmonary disease |
| Interstitial lung disease |
| Sleep-disordered breathing |
| Alveolar hypoventilation disorders |
| Chronic exposure to high altitude |
| Developmental abnormalities |
| **Pulmonary hypertension due to chronic thrombotic or embolic disease or both** |
| Thromboembolic obstruction of proximal pulmonary arteries |
| Thromboembolic obstruction of distal pulmonary arteries |
| Nonthrombotic pulmonary embolism (tumor, parasites, foreign material) |
| **Miscellaneous** |
| Sarcoidosis, pulmonary Langerhans'-cell histiocytosis, lymphangiomatosis, and compression of pulmonary vessels (adenopathy, tumor, and fibrosing mediastinitis) |

* This classification was adapted from Simonneau et al.[3]
† These conditions include thyroid disorders, type 1 glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, and splenectomy.

appears to be excellent.[32] Furthermore, resting hemodynamics do not reflect changes that may occur with exercise.[33] Thus, improvement is only partly related to a modification of resting hemodynamics in most patients.[8,33]

The NYHA functional class has been an important end point in clinical trials of pulmonary arterial hypertension, but the assignment of patients to categories is subject to the bias of investigators, a fact that limits its usefulness as an end point. The six-minute walk test, in which the patient walks as far as possible in six minutes, is a submaximal exercise test that can be performed by patients who are incapable of tolerating maximal exercise testing.[34] It is straightforward, safe, and highly reproducible and requires only inexpensive equipment. Although motivation is a key element in the test, the distance walked in six minutes has a strong independent association with mortality among patients with idiopathic pulmonary arterial hypertension.[8,34] The six-minute walk test has been widely used as a primary end point in clinical trials.

## THERAPEUTIC STRATEGIES

### BASIC THERAPY

Patients with pulmonary arterial hypertension have a restricted pulmonary circulation. Increased oxygen demand may worsen pulmonary hypertension and right heart failure.[2] However, a diagnosis of pulmonary arterial hypertension does not preclude an active lifestyle, and patients are usually advised to engage in activities appropriate to their physical capabilities in order to prevent deconditioning and attendant worsening of overall function.[35] Extreme caution concerning physical activity is advised for patients with advanced pulmonary arterial hypertension and symptoms of dizziness, lightheadedness, or severe dyspnea, because such patients are at increased risk for life-threatening syncope.[4]

Chronic hypoxemia is due to impaired cardiac output, which results in desaturation of mixed venous blood. It may also be caused by right-to-left shunting through a patent foramen ovale or a congenital heart defect. When chronic hypoxemia develops, supplemental oxygen, including ambulatory oxygen therapy, is indicated to maintain arterial oxygen saturation at a level above 90 percent.[35]

Dramatic clinical improvement in patients with right heart failure can be achieved by instituting diuretic therapy,[35] which reduces right ventricular preload. The value of cardiac glycosides in treating isolated right heart dysfunction is controversial. These agents are most useful in cor pulmonale, when left ventricular failure is also present.[35] However, since neurohormonal sympathetic activation has been demonstrated in pulmonary hypertension, digoxin may be of value because of its sympatholytic properties.[35,36] Digoxin may be most beneficial in treating pulmonary arterial hypertension with concomitant intermittent or chronic atrial fibrillation. No data from prospective randomized, double-blind, placebo-controlled trials are available to provide clear treatment guidelines.

Since pregnancy and labor increase the demand on the cardiopulmonary system, they are contraindicated in patients with pulmonary hypertension. Consequently, safe and effective contraception is always recommended for women of childbearing age who have this condition.[4] Intrauterine devices



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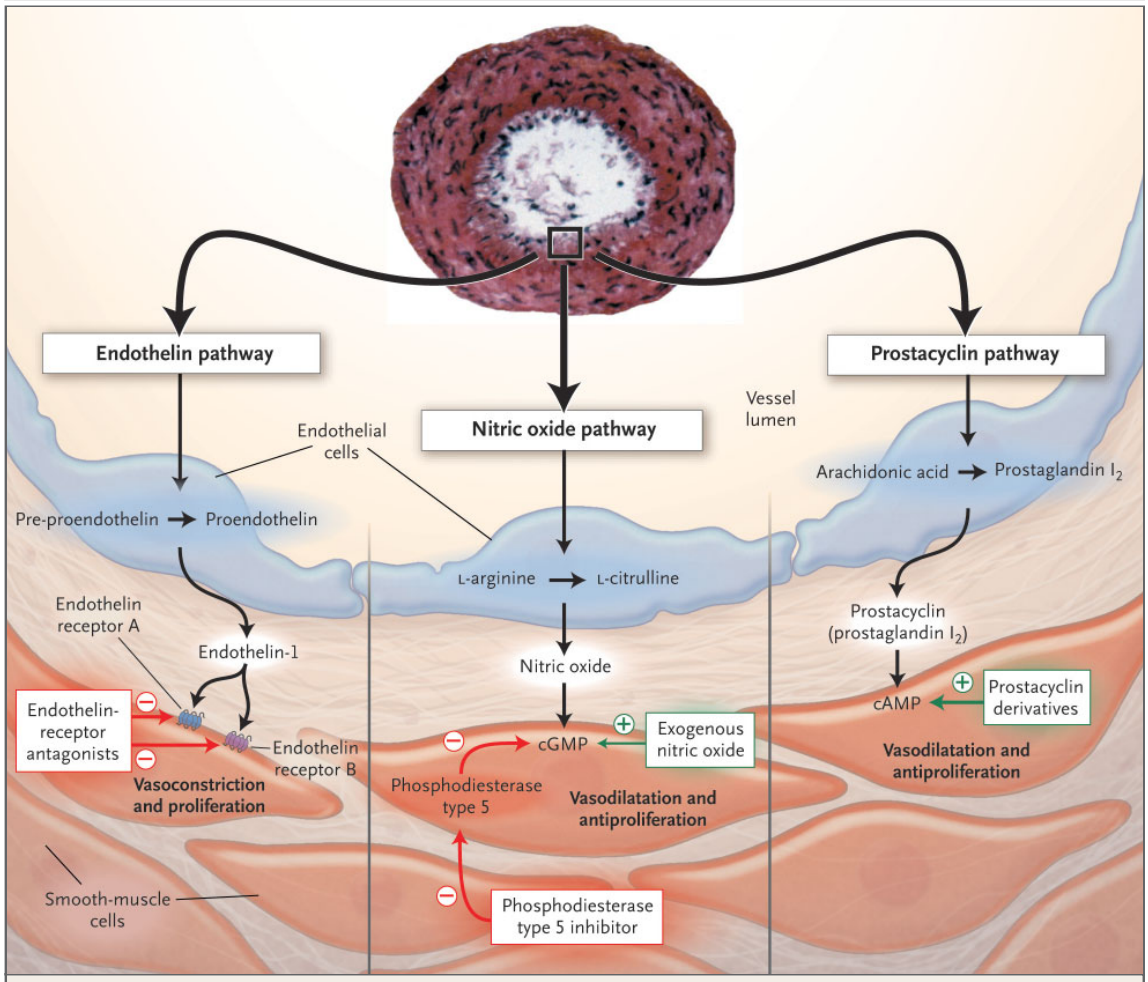


**Figure 1. Targets for Current or Emerging Therapies in Pulmonary Arterial Hypertension.**

Three major pathways involved in abnormal proliferation and contraction of the smooth-muscle cells of the pulmonary artery in patients with pulmonary arterial hypertension are shown. These pathways correspond to important therapeutic targets in this condition and play a role in determining which of four classes of drugs — endothelin-receptor antagonists, nitric oxide, phosphodiesterase type 5 inhibitors, and prostacyclin derivatives — will be used. At the top of the figure, a transverse section of a small pulmonary artery (<500 $\mu$m in diameter) from a patient with severe pulmonary arterial hypertension shows intimal proliferation and marked medial hypertrophy. Dysfunctional pulmonary-artery endothelial cells (blue) have decreased production of prostacyclin and endogenous nitric oxide, with an increased production of endothelin-1 — a condition promoting vasoconstriction and proliferation of smooth-muscle cells in the pulmonary arteries (red). Current or emerging therapies interfere with specific targets in smooth-muscle cells in the pulmonary arteries. In addition to their actions on smooth-muscle cells, prostacyclin derivatives and nitric oxide have several other properties, including antiplatelet effects. Plus signs denote an increase in the intracellular concentration; minus signs blockage of a receptor, inhibition of an enzyme, or a decrease in the intracellular concentration; and cGMP cyclic guanosine monophosphate.

or surgical sterilization has been proposed, but the procedures that are required can promote bleeding and may be impossible to perform in severely compromised patients. Vasectomy for the long-term male partner or spouse has also been proposed.

Many centers treating patients with pulmonary arterial hypertension recommend oral contraception with progesterone derivatives or low-dose estrogens, provided that the patient has no history of thromboembolic disease or thrombophilia.



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**Table 2. Functional Classification of Pulmonary Arterial Hypertension.***

| Class | Description |
|---|---|
| Class I | Pulmonary arterial hypertension without a resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope. |
| Class II | Pulmonary arterial hypertension resulting in a slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near-syncope. |
| Class III | Pulmonary arterial hypertension resulting in a marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near-syncope. |
| Class IV | Pulmonary arterial hypertension resulting in an inability to carry out any physical activity without symptoms. The patient has signs of right heart failure. Dyspnea, fatigue, or both may be present even at rest, and discomfort is increased by any physical activity. |

* This classification was modified from the New York Heart Association classification of patients with cardiac disease. It is adapted from the executive summary of the World Symposium on Primary Pulmonary Hypertension in Evian, France, in 1998.[31]

The rationale for anticoagulant therapy in a patient with pulmonary arterial hypertension is based on the presence of well-recognized risk factors for venous thromboembolism, such as heart failure, a sedentary lifestyle, and a thrombophilic predisposition. Indeed, the identification of thrombosis on postmortem examination in patients with primary pulmonary hypertension further supports this strategy.[37] However, no data actually support anticoagulant therapy specifically in patients with pulmonary arterial hypertension. Warfarin has been evaluated in only two studies (one retrospective and one prospective but nonrandomized), both involving a small number of patients.[38,39] On the basis of these limited studies, a target international normalized ratio between 1.5 and 2.5 is recommended.

### CALCIUM-CHANNEL BLOCKERS

Pulmonary-artery vasoconstriction may contribute to the pathogenesis of pulmonary arterial hypertension.[11,39] Uncontrolled studies suggest that the long-term administration of high-dose calcium-channel blockers prolongs survival among patients who have a response to this treatment (i.e., approximately 10 percent of all patients referred to pulmonary vascular units).[39-41]

Patients who may benefit from long-term therapy with calcium-channel blockers can be identified by performing an acute vasodilator challenge with the use of short-acting agents, such as intravenous prostacyclin, adenosine, or inhaled nitric oxide, during right heart catheterization.[40,41] First, a complete baseline hemodynamic evaluation is conducted while the patient is in a supine position and is breathing room air; vasodilating or inotropic agents must not have been used for at least 36 hours. After baseline measurements have been performed, the patient's response to vasodilators is tested. Nitric oxide is given through a face mask, while either prostacyclin or adenosine is administered intravenously. However, the magnitude of the short-term response to vasodilators that predicts a favorable outcome with long-term use of calcium-channel blockers remains poorly defined.[40,41] Although a reduction both of mean pulmonary-artery pressure and of pulmonary vascular resistance by at least 20 percent has been suggested for the initiation of oral therapy with calcium-channel blockers, this definition does not discriminate between patients who will have a sustained benefit (defined as achievement of NYHA functional class I or II with near-normal hemodynamics after at least one year of follow-up) and those who will not improve.[40,41]

In a retrospective analysis of 557 consecutive patients with primary pulmonary hypertension, we found that less than 7 percent had a sustained benefit from therapy with a calcium-channel blocker.[41] During acute vasodilator challenge, most patients who had a long-term response to calcium-channel blockers had a marked improvement in their pulmonary hemodynamics (i.e., the mean pulmonary-artery pressure decreased by more than 10 mm Hg, to a value lower than 40 mm Hg, with a normal or high cardiac output). Long-term therapy with a calcium-channel blocker is not recommended when these criteria are not met.

The occurrence of severe, life-threatening hemodynamic compromise during an acute vasodilator challenge with calcium-channel blockers is well documented, and these agents should not be used as first-line vasodilators when a challenge is being performed.[40] Rather, as noted above, short-acting agents — intravenous prostacyclin, adenosine, or inhaled nitric oxide — should be used. Long-term treatment with oral calcium-channel blockers



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should then be considered for patients who have a response to one of these three drugs.[1,40,41]

## PROSTACYCLIN THERAPY

### INTRAVENOUS PROSTACYCLIN

Prostaglandin $I_2$ (prostacyclin), the main product of arachidonic acid in the vascular endothelium,[42] induces relaxation of vascular smooth muscle by stimulating the production of cyclic AMP (cAMP) and inhibits the growth of smooth-muscle cells.[43] In addition, it is a powerful inhibitor of platelet aggregation.[42,44] Intravenous prostacyclin (epoprostenol) was first used to treat primary pulmonary hypertension in the early 1980s.[45] It was apparent that the absence of an acute hemodynamic response to intravenous epoprostenol did not preclude improvement with long-term therapy.[44]

A prospective randomized, open trial was conducted in 81 patients with primary pulmonary hypertension classified as NYHA functional class III or IV.[6] Participants were randomly assigned to receive either conventional therapy alone (including warfarin, diuretics, oxygen, and oral vasodilators) or conventional therapy along with an intravenous infusion of epoprostenol. After 12 weeks, patients in the group that received epoprostenol therapy had functional improvement, as demonstrated by an improved score on a six-minute walk test (an increase of 32 m in the epoprostenol group as compared with a decrease of 15 m in the conventional-therapy group, $P<0.003$). The mean pulmonary-artery pressure decreased by 8 percent in the epoprostenol group and increased by 3 percent in the control group, and the mean pulmonary vascular resistance decreased by 21 percent and increased by 9 percent in the two groups, respectively ($P<0.001$). Eight patients in the conventional-therapy group died during the study, whereas no deaths occurred in the epoprostenol group ($P=0.003$, by the two-sided log-rank test). Epoprostenol has been approved for the treatment of pulmonary arterial hypertension in North America and in some European countries since the mid-1990s.

No long-term randomized trial of epoprostenol in patients with pulmonary arterial hypertension has been conducted. Nevertheless, cohort analysis of patients with primary pulmonary hypertension who were receiving continuous intravenous epoprostenol clearly demonstrated clinical benefits for patients in NYHA functional class III or IV[7,8] as compared with historical control groups.

Despite these improvements, approximately one third of patients with primary pulmonary hypertension die within three years after diagnosis.[8] Intravenous epoprostenol improved exercise tolerance, hemodynamics, and long-term survival in a cohort of 178 patients with primary pulmonary hypertension as compared with historical controls. In the group receiving epoprostenol, the survival rate was 85 percent at one year, 70 percent at two years, 63 percent at three years, and 55 percent at five years. In the control group, the survival rate was 58 percent at one year, 43 percent at two years, 33 percent at three years, and 28 percent at five years ($P<0.001$).[8] Survival was mainly related to such baseline clinical factors as a history of right heart failure, with patients who had more severe impairment having a poorer outcome. This observation underscores the fact that death can result from a delay in the diagnosis and treatment of this disease. In addition, the prognosis appeared to be related to clinical and hemodynamic responses to long-term epoprostenol therapy. Patients whose symptoms improved sufficiently to warrant reclassification to NYHA functional class I or II after three months of receiving epoprostenol had a marked survival advantage. The absolute value of the distance of the six-minute walk at three months was a significant prognostic factor. Another trial, in which a cohort of 162 patients[7] was studied after one year of receiving epoprostenol therapy, confirmed that the patients' clinical function improved significantly, even though improvements in hemodynamic measures were modest. These findings make it clear that despite the known biologic and hemodynamic effects of epoprostenol, the mechanism by which it improves function remains largely unknown.[7,8]

Intravenous epoprostenol has obviated the need for lung transplantation in patients with severe disease.[1,2,46] A survey in the United States indicated that the condition of more than two thirds of patients who were treated with epoprostenol had improved sufficiently to allow removal of their names from the lung-transplantation waiting list.[46] However, we recommend that eligible patients who are still in NYHA functional class IV after three months of therapy remain candidates for lung transplantation.[8]

Patients with scleroderma and related disorders are prone to the development of pulmonary arterial hypertension. A multicenter randomized study of such patients showed that they had a marked improvement in exercise capacity after continuous in-



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travenous administration of epoprostenol, without an effect on mortality.[47] Uncontrolled studies indicate that patients with scleroderma who are treated with epoprostenol have a lower rate of survival than do patients with primary pulmonary hypertension who receive this treatment.[48,49] Improvements with epoprostenol have also been reported in patients who had pulmonary arterial hypertension associated with congenital left-to-right cardiac shunts,[50] portal hypertension,[51] and infection with the human immunodeficiency virus (HIV).[52,53]

Epoprostenol can be administered only by continuous intravenous infusion, owing to its short half-life in the circulation (i.e., three minutes) and its inactivation at low pH. For long-term administration, epoprostenol is infused with the use of a portable infusion pump connected to a permanent tunneled catheter inserted in the subclavian vein.[6-8] The optimal dose of epoprostenol remains undefined and varies among patients. In our experience with 340 patients who were treated with epoprostenol, the mean (±SD) dose was 21±7 ng per kilogram of body weight per minute after 1 year and 32±10 ng per kilogram per minute after 41±17 months.[54]

Despite its role in improving clinical function in some patients, epoprostenol infusion is far from the ideal treatment for pulmonary arterial hypertension, since it is complicated, uncomfortable for patients, and very costly. Common side effects of epoprostenol include jaw pain, headache, diarrhea, flushing, leg pain, and nausea, though they are generally mild and dose-related.[6-8,54] More serious complications are usually related to the delivery system.[8,48,54] The incidence of catheter-related sepsis ranges from 0.1 to 0.6 case per patient-year.[8,48] Pump failure or dislocation of the central venous catheter, leading to an interruption in drug infusion, may be life-threatening.[48] In patients who have pulmonary hypertension with prominent pulmonary-vein involvement, such as pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis, severe pulmonary edema and death may occur, presumably because of increased pulmonary perfusion in the presence of downstream vascular obstruction.[1,48,55,56]

### SUBCUTANEOUS TREPROSTINIL

The potential complications related to the central venous catheter required for intravenous infusion of prostacyclin have led to the development of treprostinil, a stable prostacyclin analogue that can be administered as a continuous subcutaneous infusion. The drug was tested in a multicenter randomized, placebo-controlled trial involving 470 patients (all in NYHA functional class II, III, or IV) who had primary pulmonary hypertension, pulmonary arterial hypertension associated with a congenital left-to-right shunt, or connective-tissue disease.[57] After 12 weeks, the study showed that patients in the overall study population who received treprostinil, as compared with those who received placebo, had a modest but significant median increase of 16 m on the six-minute walk test; patients in the primary pulmonary hypertension group had an improvement of 19 m (P=0.006). Treprostinil appeared to improve indexes of dyspnea, signs and symptoms of pulmonary hypertension, and hemodynamic measures significantly. The greatest improvement in exercise capacity was observed in patients who could tolerate the highest doses of the drug. Local pain at the infusion site was a side effect that occurred in 85 percent of the patients. Infusion-site pain precluded an increased dose in a substantial proportion of patients and led to discontinuation of treatment in 8 percent. Despite these limitations, patients with pulmonary arterial hypertension in whom life-threatening complications developed with intravenous epoprostenol have been safely switched to subcutaneous treprostinil.[58] Treprostinil has been an approved therapy for pulmonary arterial hypertension in the United States since 2002.

### ORAL BERAPROST

Beraprost sodium, the first biologically stable and orally active prostacyclin analogue,[59] is absorbed rapidly after the administration of an oral dose under fasting conditions; it reaches a peak concentration after 30 minutes and has an elimination half-life of 35 to 40 minutes.[32] In a 12-week randomized, double-blind, placebo-controlled trial involving 130 patients (all in NYHA functional class II or III) with pulmonary arterial hypertension caused by various conditions (including idiopathic pulmonary arterial hypertension, connective-tissue diseases, congenital left-to-right shunts, portal hypertension, and HIV infection),[60] patients in the overall study population who received beraprost (at a median dose of 80 μg, given four times a day) had a mean increase of 25 m on the six-minute walk test, and patients with primary pulmonary hypertension had a mean increase of 46 m (P=0.04 for both comparisons). Patients with other forms of pulmonary arterial hypertension had no significant changes in



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their exercise capacity. In the overall study population, the administration of beraprost did not significantly change cardiovascular hemodynamics. Side effects linked to systemic vasodilatation, mainly during the initial titration period, were frequent.

A 12-month randomized, double-blind, placebo-controlled trial confirmed that patients in NYHA functional class II or III who were treated with beraprost had improved scores on the six-minute walk test at three months and six months, as compared with the placebo group. However, this effect was not sustained at 9 months or 12 months, a finding that emphasizes the limitations of 3-month studies (which is the present standard for trials involving patients with pulmonary arterial hypertension).[61] Beraprost is an approved therapy for pulmonary arterial hypertension in Japan.

### INHALED ILOPROST

Iloprost is a chemically stable prostacyclin analogue that can be delivered by inhaler to patients with pulmonary arterial hypertension.[62] The delivery system produces aerosol particles of appropriate size (with an optimal mass median diameter of 0.5 to 3.0 μm) to ensure alveolar deposition, which improves pulmonary selectivity.[63] One disadvantage of iloprost is its relatively short duration of action; because of that factor, it must be inhaled as many as 6 to 12 times a day.[62,64]

A 12-week randomized, multicenter, placebo-controlled trial involving 207 patients (all in NYHA functional class III or IV) with primary pulmonary hypertension, pulmonary arterial hypertension associated with connective-tissue diseases, or inoperable chronic thromboembolic pulmonary hypertension[64] used as a combined end point a 10 percent increase in patients' scores on a six-minute walk test and improvement in NYHA functional class. Seventeen percent of treated patients reached this end point, as compared with 4 percent of the placebo group (P=0.007). The mean effect of treatment on results in the six-minute walk test was a gain of 36 m among patients in the overall study population (P=0.004) and 59 m among patients with primary pulmonary hypertension. At 12 weeks, hemodynamic values that were measured after inhalation were significantly improved in the treatment group, as compared with baseline values (P<0.001), but values were largely unchanged when measured before inhalation; values both before and after inhalation were significantly worse in the placebo group than in the iloprost group. Side effects included cough and symptoms linked to systemic vasodilatation. In addition, syncope was more frequent in the iloprost group than in the placebo group.

Although data from uncontrolled studies are encouraging,[62] the long-term efficacy of inhaled iloprost remains to be established. No studies have been performed with iloprost in the United States, where it is not an approved therapy. Iloprost has recently been approved for treating primary pulmonary hypertension in Europe.

## ENDOTHELIN-RECEPTOR ANTAGONISTS

### BOSENTAN

In addition to exerting a direct vasoconstrictor effect, endothelin-1 stimulates the proliferation of vascular smooth-muscle cells, acts as a co-mitogen, induces fibrosis, and is a proinflammatory mediator by virtue of its capacity to enhance the expression of adhesion molecules.[65-68] The effects of endothelin-1 are mediated through the $ET_A$ and $ET_B$ endothelin receptors.[67-69] Activation of $ET_A$ receptors causes sustained vasoconstriction and proliferation of vascular smooth-muscle cells, whereas $ET_B$ receptors mediate pulmonary endothelin clearance and induce the production of nitric oxide and prostacyclin by endothelial cells.[69] Bosentan is an orally active dual ($ET_A$ and $ET_B$) endothelin-receptor antagonist. Two randomized, double-blind, placebo-controlled trials have evaluated the efficacy of oral bosentan in patients with pulmonary arterial hypertension that was either primary or associated with scleroderma.[9,70]

In a pilot study, 33 patients in NYHA functional class III were randomly assigned to receive placebo or bosentan (at a dose of 62.5 mg twice daily for 4 weeks and thereafter at a dose of 125 mg twice daily for at least 12 weeks).[70] Patients receiving bosentan had a mean gain of 76 m in the six-minute walk test (P=0.02), as well as significant improvements in pulmonary-artery pressure, cardiac output, and pulmonary vascular resistance. In a subsequent study, 213 patients in NYHA functional class III or IV were randomly assigned to receive placebo or bosentan (at a dose of 62.5 mg twice daily for 4 weeks and thereafter at a dose of either 125 mg or 250 mg twice daily for at least 12 weeks).[9] The mean effect of treatment on the six-minute walk test was a gain of 44 m among patients in the overall study population (P<0.001) and 52 m among the patients with primary pulmonary hyper-



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tension. Patients receiving bosentan also had improvement in the time to clinical worsening (defined as death, lung transplantation, hospitalization for pulmonary hypertension, a lack of clinical improvement or worsening leading to discontinuation of treatment, a need for epoprostenol therapy, or atrial septostomy). No dose–response effect with respect to efficacy could be ascertained.

Bosentan is metabolized by the liver and may induce an increase in hepatic aminotransferase levels. This effect is also seen in patients receiving other endothelin-receptor antagonists, such as ambrisentan and sitaxsentan. In the bosentan trial, development of abnormal hepatic function appeared to be dose-dependent, a finding that provides a rationale for the approved dose of 125 mg twice daily.[9] Elevations in aminotransferase levels to more than eight times the upper limit of the normal range occurred in 3 percent and 7 percent of patients receiving 125 mg and 250 mg of bosentan twice daily, respectively. The drug is contraindicated during pregnancy because of its teratogenic potential.

An echocardiographic substudy involving 85 patients with pulmonary hypertension demonstrated that bosentan improved the cardiac index, right ventricular systolic function, and left ventricular early diastolic filling, leading to a decrease in right ventricular dilatation and an increase in left ventricular size.[71] Although there is some preliminary evidence of sustained efficacy with 12 months of therapy, the long-term effects of bosentan require further evaluation.[72] Bosentan, at a dose of 125 mg administered twice daily, was approved for the treatment of pulmonary arterial hypertension in North America in 2001 and in Europe in 2002. Monthly monitoring of liver function tests is mandatory. However, to date there are no reports of permanent liver dysfunction or failure with bosentan, even though more than 12,000 patients worldwide have received the drug.

### SITAXSENTAN AND AMBRISENTAN

Selective blockers of the endothelin receptor $ET_A$, such as sitaxsentan and ambrisentan, are being investigated for the treatment of pulmonary arterial hypertension.[73,74] In theory, such drugs could block the vasoconstrictor effects of $ET_A$ receptors while maintaining the vasodilator and clearance effects of $ET_B$ receptors. Cases of acute hepatitis have been described in patients taking selective $ET_A$ blockers (and proved fatal in one patient), a finding that emphasizes the importance of continuous monitoring of liver function.[73,74]

## POTENTIAL FUTURE THERAPIES

### NITRIC OXIDE

Nitric oxide is a potent endogenous, endothelium-derived vasodilator that directly relaxes vascular smooth muscle through stimulation of soluble guanylate cyclase and increased production of intracellular cyclic guanosine monophosphate (cGMP).[75] Since pulmonary arterial hypertension is associated with a defect in the production of nitric oxide and, by inference, with decreased nitric oxide–induced vasodilatation, nitric oxide has been proposed as a potential therapy.[17,75] Short-term inhalation of nitric oxide has substantial pulmonary-specific vasodilator effects in humans.[40,76] Long-term inhaled nitric oxide therapy, while showing a benefit in small series and case reports, is very cumbersome to use, so it is unlikely to be given to a large number of patients; in addition, an interruption in its administration can cause hemodynamic deterioration.[77] Anecdotal reports suggest that treatment with L-arginine, the substrate of nitric oxide synthase, reduces pulmonary-artery pressure and increases exercise tolerance in patients with pulmonary arterial hypertension.[78]

### SILDENAFIL

Another strategy for increasing the activity of endogenous nitric oxide in pulmonary arterial hypertension is to enhance nitric oxide–dependent, cGMP-mediated pulmonary vasodilatation through inhibition of the breakdown of cGMP by phosphodiesterase type 5.[75] Phosphodiesterase type 5 inhibitors, such as sildenafil, have an acute pulmonary vasodilator effect.[79,80] In a study involving patients with pulmonary arterial hypertension, short-term intravenous administration of sildenafil during right heart catheterization reduced pulmonary vascular resistance in a dose-dependent manner.[79] When this agent was combined with inhaled iloprost, augmentation of the pulmonary vasodilator effect of each single agent was noted. In patients whose condition was deteriorating despite ongoing iloprost therapy, long-term adjunctive treatment with oral sildenafil improved exercise capacity and pulmonary hemodynamics.[81] Although these findings are promising, there are few data on long-term sildenafil treatment in patients with pulmonary arterial hypertension, apart from case reports



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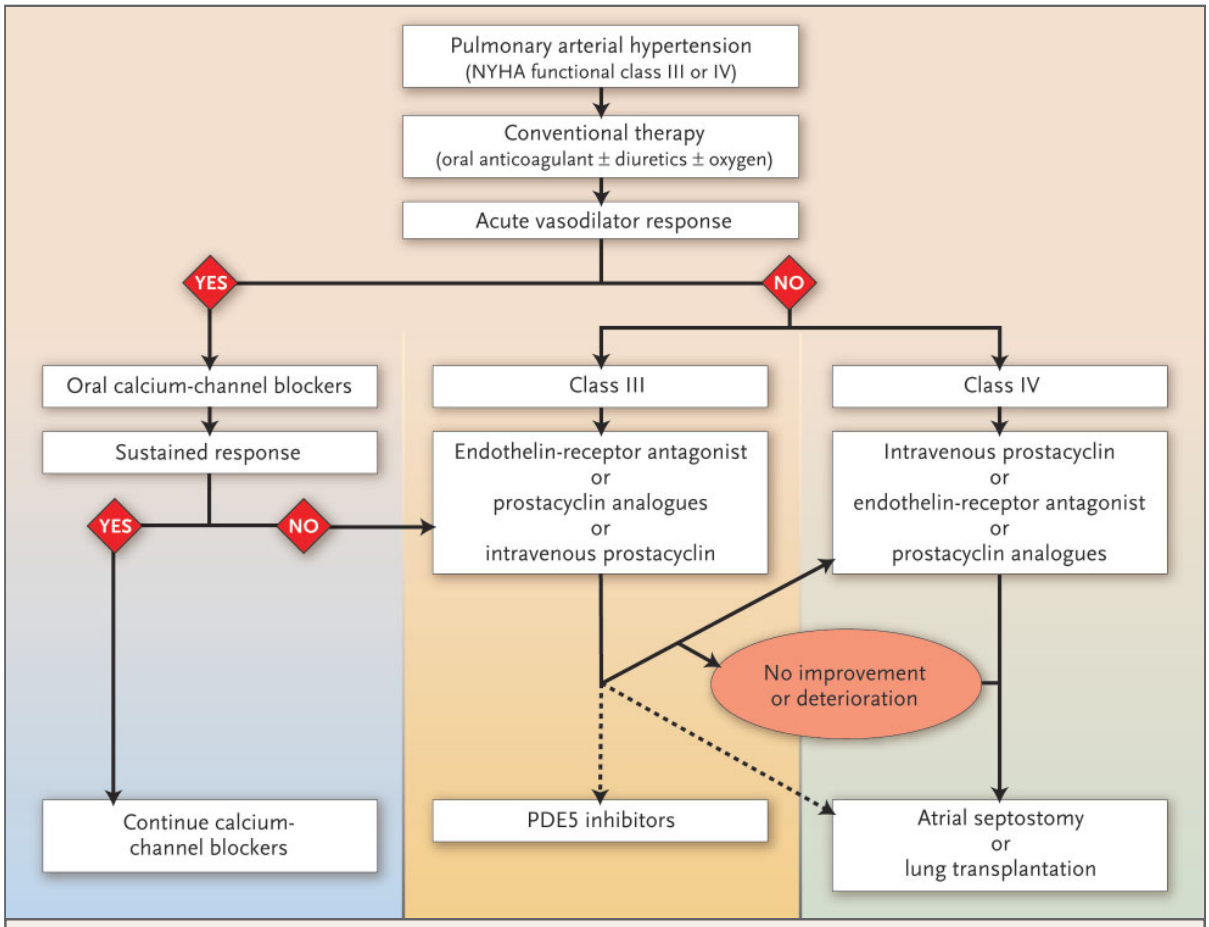


**Figure 2. Algorithm for the Treatment of Pulmonary Arterial Hypertension.**

This algorithm applies only to patients in NYHA functional class III or IV, since very few data are available for patients in NYHA functional class I or II. The treatments have been evaluated mainly in idiopathic (primary) pulmonary arterial hypertension and in cases associated with systemic sclerosis or with exposure to anorectic agents. The drugs of choice for testing of acute vasoreactivity are short-acting agents (e.g., intravenous prostacyclin, intravenous adenosine, or inhaled nitric oxide). Patients with a sustained benefit from calcium-channel blockers are defined as those in NYHA functional class I or II who have near-normal hemodynamic values after at least one year of follow-up. Most experts recommend that patients in NYHA functional class IV receive continuous intravenous epoprostenol. The experience with phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil, is preliminary, and controlled studies are ongoing to determine its efficacy and safety. The combined use of drugs with different mechanisms of action warrants further investigation. Lung transplantation is considered an option for all eligible patients who remain in NYHA functional class IV after three months of receiving epoprostenol. Atrial septostomy is proposed for selected patients with severe disease.

and short series.[82-88] The experience with sildenafil is thus preliminary, and controlled studies are in progress to determine its efficacy, side effects, and safety.[89]

### VASOACTIVE INTESTINAL PEPTIDE

Vasoactive intestinal peptide, a member of the superfamily that secretes glucagon–growth hormone–releasing factor, inhibits platelet activation and the proliferation of vascular smooth-muscle cells and acts as a potent pulmonary vasodilator. Inhalation of vasoactive intestinal peptide led to significant functional and hemodynamic improvement in eight patients with primary pulmonary hypertension.[90]

### SELECTIVE SEROTONIN-REUPTAKE INHIBITORS

Since serotonin appears to be a key player in the pathogenesis of various types of human and exper-



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imental forms of pulmonary arterial hypertension, it has been proposed that specific therapies using selective serotonin-reuptake inhibitors, such as fluoxetine, may provide protection against pulmonary hypertension.[18,91] These agents have yet to be tested in patients with pulmonary arterial hypertension.

### COMBINATION THERAPY

The combined use of drugs with different mechanisms of action in order to maximize the clinical benefit is an emerging option for the treatment of pulmonary arterial hypertension.[92] Long-term combination therapies have recently been evaluated in patients with severe disease. Adjunctive therapy with sildenafil or bosentan has produced favorable outcomes in some patients already receiving oral, inhaled, or intravenous prostacyclin analogues.[82,86,93] Conversely, a recent report indicated that the addition of long-term treatment with sildenafil had minimal effects on functional status and right-heart function in 13 patients already receiving vasodilators for pulmonary arterial hypertension (calcium-channel blockers, epoprostenol, or bosentan).[94] Additional studies with adequate statistical power are needed to determine the effect of combination therapy in patients with pulmonary arterial hypertension.[95]

## TREATMENT ALGORITHMS

Several treatments for pulmonary arterial hypertension are now approved in North America (epoprostenol, treprostinil, and bosentan) and in Europe (epoprostenol, iloprost, and bosentan). With the exception of recent data from studies of prolonged epoprostenol therapy, the long-term effects of new treatments are still unknown.[7,8] There is a substantial need for long-term observational studies evaluating the various treatments in terms of survival, side effects, quality of life, and costs. Since no data are available from head-to-head comparisons of approved therapies, the choice of treatment will be dictated by clinical experience and the availability of drugs, as well as by patients' preferences. An algorithm for the management of pulmonary arterial hypertension is shown in Figure 2. Although not discussed in depth in this review, lung transplantation[96] and atrial septostomy[97] are included in the treatment algorithm.

The treatment of pulmonary arterial hypertension has historically been restricted by a limited number of therapeutic options. Recent advances in our understanding of the pathophysiological and molecular mechanisms that may underlie pulmonary arterial hypertension, which have led to the development of new pharmacologic therapies, provide renewed hope for both patients and their physicians. Greater knowledge of this devastating disease may ultimately lead to the development of therapies that ensure a better prognosis.

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