The Pharmacologic Management of Primary Pulmonary Hypertension

It is expected that significant, new clinical trials as well as new pharmacological agents will be forthcoming in this disease state. Therefore, the following recommendations will be revised as new data becomes available. These guidelines are not intended to interfere with clinical judgment, but rather to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing.

EXECUTIVE SUMMARY

Recommendations are based on published evidence obtained from a critical literature review focused on the pharmacologic management of primary pulmonary hypertension. The quality of evidence and strength of recommendations follow the summary statement. Refer to Table 1 for a definition of grading abbreviations.

- Primary pulmonary hypertension (PPH) is a progressive disease for which there is no cure, but considerable progress in therapy has been made in both pharmacologic and surgical treatments. Based on the hemodynamic profile, PPH is classified as precapillary pulmonary hypertension or pulmonary arterial hypertension (PAH).
- Pharmacologic interventions used in PAH management have many purposes: reducing pulmonary artery pressure and pulmonary vascular resistance; increasing cardiac output; preserving right ventricular function; improving oxygen delivery; prolonging survival; and preventing thromboembolism while improving patients quality of life.
- The currently available pharmacological therapies include calcium-channel antagonists, prostacyclin (PGI_2) analogues, endothelin antagonists, and adjunctive treatments such as anticoagulation, supplemental oxygen, diuretics, digitalis, and sildenafil.
- Vasodilator therapy should be initiated in a hospital where titration can be monitored according to symptoms, blood pressure, oxygen saturation, and exercise tolerance.
- There are no hemodynamic or demographic variables which adequately predict vasoreactivity. Acute vasoreactivity studies accurately identify patients who may respond to long-term vasodilator therapy. A positive response is defined as a $\geq$25% reduction in mean pulmonary vascular resistance (PVR) coinciding with a decrease in pulmonary artery pressure (PAP), with no fall in cardiac output.
- Calcium-channel antagonists are currently the oral agents of choice for the treatment of patients with NYHA Class I and II PPH who are vasodilator responsive. (I, A) Vasodilator therapy with calcium antagonists improves symptoms, hemodynamics, right ventricular function, and survival in PPH, but only about 25% of patients are responsive and high daily doses are required. Calcium-channel antagonists should only be used in those patients with a positive acute vasodilator study. Diltiazem and dihydropyridine calcium-channel antagonists are the preferred agents.
- Epoprostenol is FDA approved for treatment of NYHA Class III and IV PPH. When compared to conventional therapy over 12 weeks, epoprostenol produced symptomatic and hemodynamic improvement, along with an improvement in survival in patients with PPH. (I,A)
- Epoprostenol has been shown to improve long-term survival in patients with PPH when compared to historical controls. (II-1, B)
- Treprostinil is FDA approved for treatment of NYHA Class II, III, and IV PPH. Compared to placebo, continuous subcutaneous infusion of treprostinil statistically improved exercise capacity, hemodynamic response, and physical quality of life. (I, A) Further long-term studies are required to determine the effect on patient survival.
- Bosentan is effective for increasing exercise capacity and improving hemodynamics in patients with NYHA Class III or IV PPH and is well-tolerated at a dose of 125 mg twice daily. (I, A) The effect of bosentan on survival has not been systematically studied to date. Due to its lack of long-term safety and efficacy data and absence of hard endpoints, it is difficult to recommend bosentan as first line therapy in Class III or IV PPH patients.
- There is currently no evidence supporting the use of epoprostenol, treprostinil, and/or bosentan in combination for the treatment of PPH.
- All patients with PPH should receive anticoagulation. Warfarin is the anticoagulant of choice and should be dosed to a target INR of 2-3. (II-1, A)

- Supplemental oxygen is of benefit in patients with PPH who are hypoxic. The criteria for prescribing oxygen in PPH are similar to those used for chronic obstructive pulmonary disease. (III, C)
- Digoxin produces favorable hemodynamic effects in patients with right ventricular failure and PPH. (II-1, C) Long-term efficacy and safety data is lacking, therefore treatment with digoxin is controversial.
- Diuretics are frequently required to reduce excessive edema and fluid overload in patients with right heart failure due to PPH. Diuretics are particularly beneficial when hepatic congestion and ascites are present. (III, C)
- Sildenafil is not currently approved by the FDA for treatment of PPH, however a few small open-label, randomized, controlled trials and case reports suggest it may have a beneficial hemodynamic and symptomatic effect for these patients. Sildenafil may be considered as an adjunct measure for patients without adequate response to maximized therapeutic regimens when no other treatment options are available. (I, C)
- All PPH patients should be considered as candidates for pneumococcal and influenza vaccination. (III, C)
- Women of child-bearing age with PPH require contraceptive advice. (III,C)
- No cost-effectiveness trials have been completed to date which support choosing one of these agents over the other.

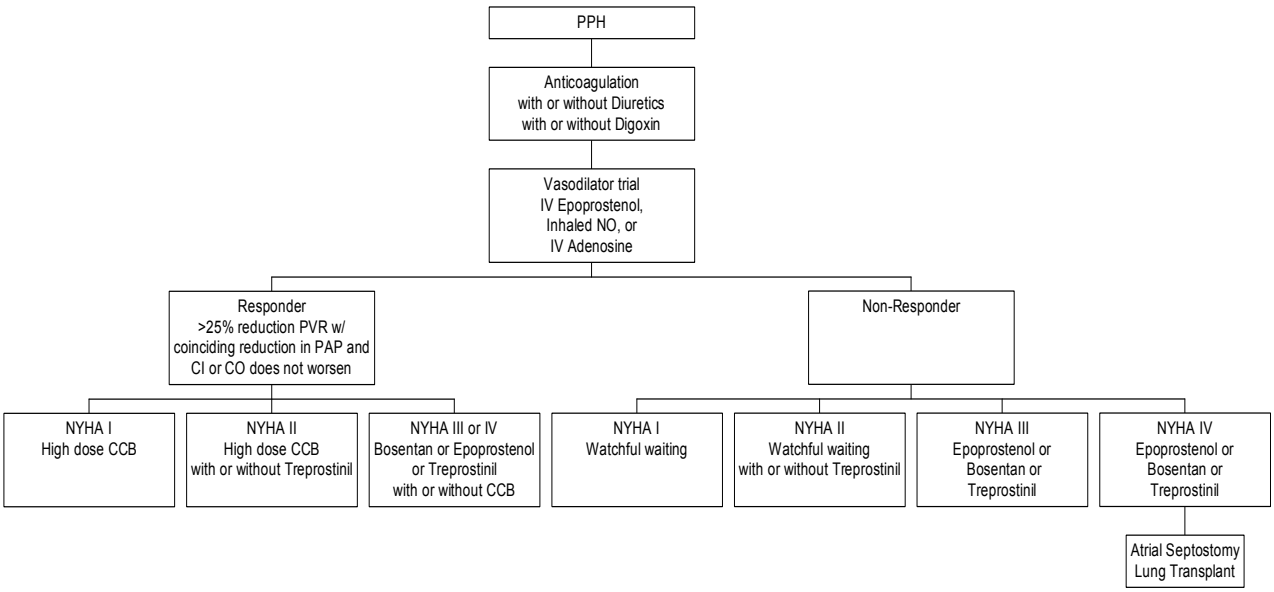
Table 1. Evidence Rating Used by US Preventative Services Task Force

Quality of Evidence
I: Evidence obtained from at least one properly randomized controlled trial.
II-1: Evidence obtained from well-designed controlled trials without randomization.
II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3: Evidence obtained from multiple time series studies with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III: Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.
Strength of Recommendation
A: There is good evidence to support that the intervention be adopted.
B: There is fair evidence to support that the intervention be adopted.
C: There is insufficient evidence to recommend for or against the intervention, but recommendations may be made on other grounds.
D: There is fair evidence to support that the intervention be excluded.
E: There is good evidence to support that the intervention be excluded.

Algorithm: Pharmacologic Management of Primary Pulmonary Hypertension

Goals of Therapy

1. Improve overall quality of life
2. Improve survival for patients
3. Provide an effective "bridge" while awaiting more effective therapies



Sildenafil may be considered as an adjunct measure for patients without adequate response to maximized therapeutic regimens when no other treatment options are available.

Introduction

Primary pulmonary hypertension is a pulmonary vascular disease distinguished by an elevation in mean pulmonary artery pressure and pulmonary vascular resistance without a demonstrable cause. PPH is defined in the National Institutes of Health (NIH) Registry as a mean pulmonary artery pressure (PAP) of greater than 25 mmHg at rest, or greater than 30 mmHg with exercise, excluding left-sided cardiac valvular disease, myocardial disease, congenital heart disease, and any clinically important respiratory, connective-tissue, or chronic thromboembolic diseases.[1] It should be noted that in the elderly population, pulmonary arterial pressure may be higher, particularly during exercise due to decreased compliance of the pulmonary artery as well as increased pulmonary vascular resistance (PVR).[2] Thus, in healthy elderly patients, exercise-induced pulmonary hypertension may be categorized as postcapillary.[3] Since this can be considered a normal age-related response, these subjects may not be considered for aggressive therapy.[3] Based on the hemodynamic profile, PPH is classified as precapillary pulmonary hypertension. This hemodynamic profile can be described as systolic, diastolic, and mean pulmonary arterial pressures higher than normal; normal mean pulmonary capillary wedge pressure; significantly elevated pulmonary vascular resistance; and pulmonary arterial end diastolic pressure significantly higher than the pulmonary capillary wedge pressure.[3] The clinical conditions that are usually encountered in precapillary pulmonary hypertension are listed in Table 2. These guidelines were developed for patients with PPH, however they may also be used when considering treatment modalities for clinical conditions contributing to precapillary pulmonary hypertension. PPH is a progressive disease for which there is no cure, but considerable progress in therapy has been made in both pharmacologic and surgical treatments. Pharmacologic interventions used in pulmonary arterial hypertension management have many purposes: reducing pulmonary artery pressure and pulmonary vascular resistance; increasing cardiac output; preserving right ventricular function; improving oxygen delivery; and preventing thromboembolism while improving patients quality of life. The currently available pharmacological therapies include calcium-channel antagonists, prostacyclin (PGI_2) analogues, endothelin antagonists, and adjunctive treatments such as anticoagulation, supplemental oxygen, diuretics, digitalis, and sildenafil.

These guidelines will address the use of pharmacologic intervention in PPH. It will present data from recent clinical trials and extrapolate the results to the Veteran population.

Table 2. Clinical Conditions Encountered in Hemodynamic Categories of Pulmonary Hypertension

Precapillary Pulmonary Hypertension

- Primary pulmonary hypertension
- Pulmonary hypertension associated with collagen vascular disease
- Eisenmenger syndrome
- Liver disease (portal hypertension)
- Human immunodeficiency viral infection
- Appetite suppressants
- Persistent pulmonary hypertension of the newborn
- High-altitude pulmonary hypertension
- Neurogenic pulmonary hypertension
- Thromboembolic pulmonary hypertension
- Peripheral pulmonary artery branch stenosis

Background

It is beyond the scope of this review to define the diagnosis of PPH, however the functional classification of the disease will be reviewed as this will aid in interpretation of the results of the clinical trials. Table 3 lists the New York Heart Association (NYHA) functional classification according to the World Health Organization (WHO).

Acute vasoreactivity studies accurately identify patients who may respond to long-term vasodilator therapy. A positive response is defined as a ≥25% reduction in mean PVR coinciding with a decrease in PAP, with no fall in cardiac output (CO), although a definition of ≥20% reduction has been used in some clinical trials.[3,4,5] Drugs recommended for acute vasodilatory challenge are intravenous prostacyclin, intravenous adenosine, and inhaled nitric oxide. The NIH Registry of patients with PPH demonstrates that the hemodynamic variables that are the most predictive of prognosis are those indicative of right ventricular function. Therefore, right atrial pressure, PVR, and cardiac index (CI) are often frequently included as efficacy measures in clinical trials.[1] Other efficacy measures commonly used in PPH trials are PAP, survival, exercise capacity or tolerance, quality of life, and tolerability of the agent studied.

Table 3. NYHA Functional Classification of Pulmonary Hypertension

Class I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope

Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope

Class III: Patients with pulmonary hypertension resulting in pronounced limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope

Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

Vasodilator Therapy

The rationale for using vasodilators in PPH is based on the theory that vasoconstriction is one of the main features of the disease. Unfortunately, clinicians cannot predict which patients will respond to vasodilator therapy based on hemodynamic characteristics.[6] Therefore, it is imperative to evaluate pulmonary vasoreactivity as the response to vasodilator challenge predicts which patients are likely to respond to long-term oral therapy with calcium-channel antagonists.[7] Vasodilator therapy should be initiated in a hospital where titration can be monitored according to symptoms, blood pressure, oxygen saturation, and exercise tolerance. Many different vasodilators such as hydralazine, diazoxide, isosorbide dinitrates, α-adrenergic blockers, and β-adrenergic agonists such as isoprenaline have been studied in patients with PPH, but without success. Currently, calcium-channel antagonists, PGI_2 analogues, and bosentan are the only effective vasodilator pharmacotherapy.

Calcium-channel antagonists

Calcium-channel antagonists are currently the oral agents of choice for the treatment of patients with NYHA Class I and II PPH. Vasodilator therapy with calcium antagonists improves symptoms, hemodynamics, right ventricular function, and survival in PPH, but only about 25% of patients are responsive and high daily doses are required.[8,9,10] Calcium-channel antagonists should only be used in those patients with a positive acute vasodilator study as these agents are effective in the presence of vasoconstriction, but not in its absence. Diltiazem and dihydropyridine calcium-channel antagonists are the preferred agents. Table 4 lists dosage ranges, routes of administration, and half-lives of the most frequently used calcium-channel antagonists for PPH. Verapamil is not recommended for use due to its negative inotropic effects.[11] The value of treatment with calcium-channel antagonists long-term was summarized in a meta-analysis of 8 clinical trials investigating nifedipine. This study showed that a reduction in PAP occurred in 7 of 8 trials, was a dose-related effect, and correlated with subjective clinical improvement.[12] A 5-year follow-up study on 64 patients showed that 94% of patients who responded to calcium-channel antagonists survived for 5 years, compared with a 5-year survival rate of 38% as reported by the NIH Registry for patients with PPH not treated with calcium-channel antagonists.[9] Treatment-limiting adverse effects experienced with calcium-channel antagonists are symptoms such as depressed myocardial contractility, hypoxemia due to ventilation-perfusion mismatching, and systemic hypotension, which can require cessation of therapy even in patients who are acute responders.[13]

Table 4. Calcium-channel Antagonists Used in PPH

Drug	Route	Dose Range	Half-life
Nifedipine	Oral	30-240 mg/day	2-5 hr
Diltiazem	Oral	120-900 mg/day	2-4.5 hr

Epoprostenol (Flolan®)

Epoprostenol (prostacyclin, PGX, PGI_2) is a potent short-acting vasodilator and platelet aggregation inhibitor. It was approved by the FDA in 1995 and is indicated for the long-term treatment of NYHA class III and IV PPH. Clinical trials in patients with PPH have shown symptom reduction, increased exercise tolerance, improved quality of life, and an increased survival with a continuous infusion of epoprostenol.[5,14,15,16,17,18] Continuous treatment with epoprostenol has also been shown to delay the need for lung transplantation.[19] Clinical experience and long-term outcome data support the use of epoprostenol.[16,17,18,20] Similar long-term outcomes have not been evaluated for other newer vasodilators. A review of pertinent epoprostenol trials can be found in Appendix A.

Therapy with epoprostenol can be complex for patients and caregivers. Patients and caregivers should be interviewed and their potential for compliance should be assessed. Because of its short half-life of approximately six minutes, epoprostenol must be given by continuous intravenous infusion using a portable infusion pump and requires placement of a permanent central venous catheter. Extensive education must be provided to patients and caregivers to assure that they understand how to aseptically prepare and administer the drug, monitor for efficacy of treatment, and respond in the event of pump malfunction. Along with the adverse effects of the drug itself, patients are also at risk for adverse events secondary to the drug delivery system. Septicemia, local infections, irritation, and bleeding have all been reported in patients being treated with epoprostenol. If there is concern with the patient and/or caregivers' ability to comply with the regimen, an alternative treatment modality may be warranted (e.g. oral bosentan).

Upon initiation of treatment with epoprostenol, patients must undergo an acute dose ranging trial, which will determine the chronic infusion rate. After placing a right heart catheter, the infusion is started at 2 ng/kg/min, and increased by 2 ng/kg/min at intervals of at least 15 minutes until doses limiting adverse effects are experienced. The most common adverse effects include nausea, vomiting, jaw pain, anxiety, hypotension, bradycardia, and flushing. The mean maximum dose in clinical trials, which did not produce dose-limiting effects, was 9.2 +/- 0.3 ng/kg/min. Once the maximum tolerated dose is determined, the chronic infusion should be administered at a rate 4 ng/kg/min less than the maximum dose. If the maximum tolerated dose is less than 5 ng/kg/min then one-half of the maximum tolerated dose should be the starting dose for chronic infusion. Patients may require periodic dosage increments during sustained worsening of PPH symptoms. Dosage increases should be performed in a monitored setting in increments of 1 to 2 ng/kg/min at intervals of at least fifteen minutes, allowing assessment of clinical response.[21]

Treprostinil (Remodulin®)

Treprostinil is a prostacyclin analog delivered by continuous subcutaneous infusion that was approved by the FDA on May 21, 2002 for treatment of pulmonary arterial hypertension in patients with NYHA class II, III, and IV symptoms. Treprostinil, like epoprostenol, is thought to have vasodilatory, anti-proliferative, anti-aggregatory, and anti-inflammatory effects on the pulmonary vasculature.[22] Treprostinil has a pharmacokinetic advantage over epoprostenol with a longer half-life and greater stability at room temperature. This allows for a subcutaneous infusion and eliminates the need for central venous access as with epoprostenol.[22,23,24] A review of pertinent treprostinil trials can be found in Appendix B.

FDA approval of this medication was based upon the results of two international, double-blind, placebo-controlled studies that were combined for results involving 470 patients from 40 different medical centers.[23,25] The results of the two studies, separately, found no statistically significant differences between treatment and placebo for primary endpoints. However, when combined a statistical benefit in 6 minute walking time was apparent in the treprostinil treatment group. Although the statistical benefit has been demonstrated, the clinical benefit may not be as obvious. During further analysis of the results, patients receiving higher treatment doses and patients who had greater symptoms at baseline had a greater response to treatment. Statistical improvements were also reported for dyspnea and physical quality of life, but not global quality of life. No trials have been conducted comparing treprostinil and the other available prostacyclin, epoprostenol. No available studies to date have shown a survival benefit with treprostinil treatment versus placebo, but there are no studies that have been designed or powered to evaluate this outcome.

Treprostinil was dosed at 1.25 ng/kg/min and titrated to the maximum tolerated dose in clinical trials. Adverse events reported in these studies were frequent and resulted in discontinuation of therapy in about 8% of patients receiving treatment. The most common adverse events reported in 80-90% of patients are infusion site pain, infusion site reactions, and bleeding or bruising at the site of reaction.[23,25] Other, less frequent reactions include headache, flushing, jaw pain, peripheral edema, and diarrhea.

A potential role for treprostinil is for patients not tolerating or with complications associated with epoprostenol. One open, uncontrolled study with 8 patients was successful in transitioning patients who were not tolerating IV epoprostenol to subcutaneous treprostinil with minimal side effects, other than injection site pain, and without relapsing symptoms for four to eleven months.[24] All patients enrolled in the study reported an improved sense of comfort. More supporting literature for this transition is required to determine effects on disease outcome.

Bosentan (Tracleer®)

Patients with pulmonary arterial hypertension have been shown to have elevated plasma and lung tissue concentrations of endothelin-1 (ET-1), a neurohormone with potent vasoconstricting, proliferative, profibrotic, and pro-inflammatory effects.[26,27] Bosentan is a competitive antagonist at endothelin receptor subtypes ET_A and ET_B, with slightly higher affinity for ET_A receptors. ET_A receptors are found in vascular smooth muscle and ET_B receptors are found in the brain, endothelium, and smooth muscle cells.[28] The antagonism of the actions of ET-1 may lead to a reduction in PVR and the effects of chronic hypertension on vascular remodeling.[29] Bosentan is FDA approved for the treatment of pulmonary arterial hypertension in patients with NYHA Class III or IV symptoms. It is only available after the patient is enrolled in the Tracleer® Access Program. A review of pertinent bosentan trials can be found in Appendix B.

Bosentan has been studied in 2 double-blind, randomized, placebo controlled trials for the treatment of pulmonary arterial hypertension. Bosentan is effective for increasing exercise capacity and improving hemodynamics in patients with NYHA Class III or IV PPH and is well-tolerated at a dose of 125 mg twice daily.[30,31] Limitations of these studies are small sample sizes, the use of surrogate endpoints, and the absence of long-term data in this disease state. The effect of bosentan on survival has not been systematically studied to date.

Safety data on bosentan was obtained from 12 clinical studies in 777 patients with PAH, and other diseases (primarily chronic heart failure). Treatment discontinuation due to adverse events in patients with PAH were more frequent for bosentan (5%; 8/165 patients) than for placebo (3%; 2/80 patients). The only cause of discontinuation >1%, and occurring more often on bosentan was abnormal liver function. Other common adverse effects are headache nasopharyngitis, flushing, lower extremity edema, and hypotension.

Other Adjunctive Therapies

Anticoagulation

Anticoagulation is recommended by most reviews for patients with PPH due to an increased risk of thrombosis and thromboembolism associated with poor pulmonary blood flow, dilation of the right heart chambers, venostasis, and limited physical activity.[3,32] Warfarin is the anticoagulant of choice and is usually dosed to a targeted INR of 2-3. Heparin and low molecular weight heparins have not been thoroughly evaluated in this setting. Two non-randomized trials have demonstrated a statistically significant prolonged survival in patients receiving warfarin despite response or lack of response to other medications.[9,33]

Supplemental Oxygen

Some PPH patients experience arterial oxygen desaturation with activity. Supplemental oxygen is of benefit in patients with PPH who are hypoxic. The criteria for prescribing oxygen in PPH are similar to those used for chronic obstructive pulmonary disease.[34,35]

Digitalis

The efficacy of cardiac glycosides in the treatment of PPH is unknown, therefore treatment with digoxin is controversial. Some authors have recommended using digoxin in combination with calcium-channel antagonists to negate their negative inotropic effects.[8] Rich and colleagues reported digoxin produced favorable hemodynamic effects in patients with right ventricular failure and PPH, however long-term efficacy and safety data is lacking.[36]

Diuretics
Diuretics are frequently required to reduce excessive edema and fluid overload in patients with right heart failure. Diuretics are particularly beneficial when hepatic congestion and ascites are present.[37] Small reductions in intravascular volume can result in profound hypotension in some patients so caution is necessary when initiating therapy.

Sildenafil (Viagra®)
Sildenafil is not currently approved by the FDA for treatment of primary pulmonary hypertension. However, there are several small, open-label, randomized controlled trials and case reports evaluating the hemodynamic effects of sildenafil that suggest it may be beneficial for treatment of this condition. By blocking phosphodiesterase 5(PDE-5), sildenafil increases the availability of cyclic guanosine monophosphate (c-GMP) and enhances vascular sensitivity to nitric oxide.[38,39,40] Hemodynamic improvements that have been reported include increases in the cardiac index and decreases in pulmonary vascular resistance, pulmonary artery pressure,[38,39,40,41] and the ratio of pulmonary to systemic vascular resistance.[42] Several cases reported significant improvement in the patients' clinical condition, as well, returning to NYHA class II from NYHA class III.[39,43] Doses ranged from 12.5mg per day to 100mg five times per day. Effects appear dose related based upon available literature but more studies are needed to confirm this finding. When used in combination with inhaled NO and inhaled iloprost, sildenafil has been reported to increase the area under the curve for reduction in PVR over monotherapy with these agents.[41,44] All of the cases and trials published thus far have suggested positive benefits with the use of this agent, however, this may reflect a publication bias in that cases or trials where sildenafil is not effective are not being reported or published. Due to the ease of administration, lower treatment cost compared to other available agents, and lack of available treatments, sildenafil has been increasingly used off-label for this indication. Despite the promising data, at this time there are no trials that are appropriately blinded, of adequate duration, and of adequate power to determine the overall clinical benefit and role of this medication for the treatment of PPH.

Cost Comparison

To date, no cost-effectiveness trials have been conducted on the various pharmacological treatments for PPH, therefore economic issues currently do not favor one approach over the other. Table 5 compares the direct medication costs of the available pharmacologic treatment options.

Table 5. Acquisition Costs and Pharmacology of Various Pharmacologic Treatments of PPH

Treatment	Cost	Formulation	Dose	MOA	Adverse Events
Epoprostenol (Flolan®)	FSS Pricing Unavailable	Continuous Intravenous	Initial dose of 2 ng/kg/min Increase by 2 ng/kg/min until symptomatic improvement or limited by side effects Wait at least 15 min btw dosage increases	Prostacyclin analogue	Flushing Headache Jaw pain Diarrhea Nausea
Bosentan (Tracleer®)	$21,638 per annum	Oral	Initial dose of 62.5 mg twice daily for 4 weeks with food, titrated to maintenance dose of 125 mg twice daily with food Max dose 250 mg/day; doses greater than 125 mg twice daily do not offer additional symptom benefit	Endothelin antagonist	Abnormal liver function Headache Nasopharyngitis Flushing Lower extremity edema Hypotension
Treprostinil (Remodulin®) UT-15	~$30,000 per annum[1]	Continuous Subcutaneous	Initial dose of 1.25ng/kg/in for the first 4 weeks. Increase by no more than 2.5ng/kg/min per week until desired effect Doses higher than 40ng/kg/min have not been well studied.	Prostacyclin analogue	Infusion site reactions (8% discontinuation rate) Jaw pain Flushing Headache Peripheral Edema Diarrhea
Sildenafil (Viagra®)	$800-$8000 per annum	Oral	12.5mg once daily-100mg five x/day	PDE-5 inhibitor Enhances pulmonary vascular sensitivity to NO	Flushing Dizziness Headache Nasal congestion

1. Estimated cost based on average doses used in trials for 70kg male; Vials are stable for 14 days from initial use

Discussion

The optimal treatment for PPH is not clearly defined due to incomplete clinical evidence and the lack of patients available to conduct necessary clinical trials. There is an increasing need for head-to-head trials comparing the growing number of new therapeutic options.

Epoprostenol remains the most extensively studied agent for PPH, and the only treatment option for patients with severe symptomatology that has supporting evidence of improved survival when used long-term.

In available studies, treprostinil improved 6 minute walking distance by 3% during treatment compared to baseline and epoprostenol has increased 6 minute walking distance by 35-50% compared to baseline. Due to the lack of long-term safety and efficacy data and absence of hard endpoints, it is difficult to recommend treprostinil or bosentan as first line therapy in Class III or IV PPH patients. However, as treatment can sometimes be complicated by the requirement of a permanent central line for chronic epoprostenol therapy, the development of an effective oral or subcutaneous agent, such as bosentan or treprostinil respectively, is attractive to both patients and clinicians.

The decision between available treatment options for PPH should be based on evidence supported in clinical trials, individual patient characteristics, and patient and caregiver preference. Epoprostenol, treprostinil, and bosentan are all extremely costly agents, ranging from $30,000 to $100,000 per annum. No cost-effectiveness trials have been completed to date which support choosing one of these agents over the other.

Appendix A. Results of Clinical Trials for Epoprostenol

Trial	Design*	Inclusion criteria	N	Drug	Duration	Results
Jones et al. (1987)[14]	OL, UC	Severe PPH unresponsive to oral vasodilators, all referred for heart and lung transplant	10	intravenous epoprostenol	1-25 months	CI ↑ from 1.8 to 2.2 l/min/m2 (ns); walking speed ↑ from 2.5 to 4.3 km/hr (p<0.01)
Rubin et al. (1990)[4]	OL, RDP	PPH with failure of previous vasodilator therapy	24	intravenous epoprostenol	8 weeks	PVR ↓ from 21.6 units to 13.7 units (95% CI, -13.1 to -2.2; P = 0.022); ↑ 6-min walk distance from 246 to 378 m (p=0.011); ↑ CO from 3.3 to 3.9 L/min (p=0.02)
Barst et al. (1994)[5]	OL, MC, UC, historical controls for survival	PPH	18	intravenous epoprostenol, all treated with anticoagulants	≥ 18 months	6-min walk distance at 6 months, 370 +/- 119 meters compared with baseline (p < 0.001); distance at 18 months, 408 +/- 138 meters (p = 0.02) compared with baseline; CI at 6 mos. ↑ 18% (95% CI, 0.1% to 36.7%; p =0.02); at 6 mos mean PAP ↓ 9% (CI, 1.4% to 15.7%; p= 0.03); at 6 mos PVR ↓ 26% (CI, 6.1% to 46.3%; p= 0.02); The improvements in CI and PVR were maintained at 12 mos. (27% ↑ [CI, 1.3% to 51.9%; [p= 0.05] and 32% ↓ [CI, 9.7% to 53.6%; p= 0.02] compared with baseline, respectively); Survival was improved in NYHA class III and IV patients who received continuous prostacyclin (p=0.045) when compared to historical controls
Barst et al. (1996)[15]	OL, RDCP, MC	PPH in NYHA functional Class III or IV despite optimal medical therapy	81	intravenous epoprostenol plus conventional therapy compared with conventional therapy alone	12 weeks	6-min walk distance for Tx group 362m at 12 weeks vs. 315m at base line, compared with conventional therapy alone 204m at 12 weeks vs. 270m at base line (p< 0.002); mean PAP for the epoprostenol and control groups were -8 percent and +3 percent, respectively (95 percent confidence interval, -10.7 to -2.6 mm Hg; p< 0.002); PVR for the epoprostenol and control groups were -21 percent and +9 percent, respectively (95 percent confidence interval, -7.6 to -2.3 mm Hg/liter/min; P < 0.001); Improvement in survival at 12 weeks (P=0.003)
Shapiro et al. (1996)[20]	OL, NRP, UC, historical controls for survival	PPH in NYHA functional Class III or IV	69	intravenous epoprostenol	0.9-1.9 yrs	At 3 mos. CO ↑ 4.0 to 4.7 L/min (p<0.02); The 1-, 2- and 3-year survival rates were improved when compared to historical control subjects.
McLaughlin et al. (1998)[16]	OL, NRP, UC	PPH in NYHA functional Class III or IV despite optimal medical therapy	27	intravenous epoprostenol	12-24 months, mean period of 16.7 months	PVR ↓ 53% (p<0.001); PAP ↓ 22% (p<0.001); CO ↑ 67% (p<0.001); Improvement in NYHA functional class compared with baseline (p<0.001); exercise duration ↑ 142% (p<0.001)
Sitbon et al. (2002)[17]	OL, NRP, UC, historical controls for survival	PPH in NYHA functional Class III or IV despite optimal medical therapy	178	intravenous epoprostenol	mean 26 months (range 0.5 to 98 months)	6-min walk distance ↑ 125m from baseline at 3 mos. (p<0.001); survival at 1,2,3,and 5 years were 85%, 70%, 63%, and 55%, respectively, as compared to 58%, 43%, 33%, and 28% in the historical control group (p<0.0001).
McLaughlin et al. (2002)[18]	Observational	PAH in NYHA functional Class III or IV despite optimal medical therapy	162	intravenous epoprostenol	Mean 36.3 months	Observed survival at 1,2,and 3 years with epoprostenol therapy was 87.8%, 76.3%, and 62.8% respectively (p<0.001) when compared with historical controls.

*OL=open label; UC=uncontrolled; MC=multicenter; RDP=randomized prospective; RDCP=randomized controlled prospective; NRP=non-randomized prospective

Appendix B. Results of Clinical Trials for Bosentan and Treprostinil

Trial	Design*	Inclusion criteria	N	Drug	Duration	Results
Simomneau, et al. (2002)[23]	RDB, PC, MC	PPH or PAH associated with connective-tissue disease or associated with congenital systemic to pulmonary shunts	470	Continuous subcutaneous infusion of treprostinil 1.25 ng/kg/min, titrated to max tolerated dose or 22.5 ng/kg/min	12 weeks	Difference in median distance walked btw treprostinil and placebo gps. at week 12 was 16 meters (95% CI, 4.4m to 27.6m; p=.006); Statistically significant improvement in CI, stroke index, mixed venous oxygen, right atrial pressure, PVR, and PAP; ↓ Borg Dyspnea score form median 4.3 at baseline to 3.2 at 12 weeks for treprostinil vs. 4.4 at baseline to 4.2 at 12 weeks for placebo (p<0.0001); QOL did not improve in global dimension score, but did in physical dimension score (p=0.0064)
Rubin, et al. (2002)[26]	RDB, PC	Symptomatic, severe PAH either PPH or associated with connective-tissue disease; patients in NYHA functional Class IV were stable	213	oral bosentan 62.5 mg twice daily for 4 weeks or placebo, followed by 125 or 250 mg bosentan twice daily for 12 weeks	16 weeks	↑ 6-min walk distance by 35 m in combined bosentan gps vs. 8 m ↓ in placebo gp. (95% CI, 21-67; p<0.001); mean treatment effect at week 16 for Borg dyspnea index -0.6 in favor of bosentan (95% CI, -1.2 to -0.1); 42% of bosentan pts. Were in better NYHA functional Class by week 16, resulting in mean treatment effect of 12% (95% CI, -3 to 25 percent); bosentan ↑ time to clinical worsening vs. placebo (p=0.002)
Channick, et al. (2001)[27]	RDB, PC	Symptomatic, severe PAH in NYHA functional Class III or IV; either PPH or pulmonary hypertension de to scleroderma	32	oral bosentan 62.5 mg twice daily for 4 weeks or placebo, followed by 125 mg bosentan twice daily for a minimum of 12 weeks	≥16 weeks	↑ 6-min walk distance by 70 m in 12 weeks in bosentan gp. vs. 6 m ↓ in placebo gp. (95% CI, 12-139; p<0.021); ↑ CI in bosentan gp. (95% CI, 0.6-1.4; p<0.0001); ↓ PVR in bosentan gp. (difference-415 [-608 to -221]; p=0.0002); number and nature of adverse events did not differ btw gps.

*MC=multicenter; RDB=randomized double-blind; PC=placebo-controlled

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