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REVIEW

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Pulmonary arterial hypertension: a current review of pharmacological management

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Abstract

Pulmonary hypertension (PHTN) is a rare and devastating disease characterized by progressive increases in pulmonary arterial pressure and pulmonary vascular resistance, which eventually leads to right ventricular failure and death. At present there is no cure for pulmonary arterial hypertension (PAH); however over the past decade targeted pharmaceutical options have become available for the treatment of PAH. Prior to evaluation for therapeutic options a definitive diagnosis of pulmonary arterial hypertension must be made via comprehensive physical exam and definitive diagnostic testing. Screening test of choice remains echocardiography and gold standard for definitive diagnosis is right heart catheterization. Once the establishment of a diagnosis of PAH is made therapeutic options may be a possibility based on a diagnostic algorithm and disease severity of the PAH patient. There are different classes of medications available with different mechanisms of actions which have a vasodilatory effect and improve exercise tolerance, quality of life as well as survival.

Key words: pulmonary arterial hypertension, phosphodiesterase type 5 inhibitors, endothelin receptor antagonist, prostacyclin analogues, right heart catheterization

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Introduction

Pulmonary hypertension (PHTN) is a rare and devastating disease characterized by progressive increases in pulmonary arterial pressure and pulmonary vascular resistance which eventually leads to right ventricular failure and death [1]. Symptomatically it is characterized by increasing shortness of breath and worsening exercise tolerance. It may due to various etiologies such as left heart disease, parenchymal lung disease, chronic thromboembolic disease, hematologic disorders or it may be idiopathic in nature though the clinical picture of these patients is similar [2]. More specifically pulmonary arterial hypertension (PAH) is due to direct injury to the pulmonary vessels and vascular bed. At present there is no cure for PAH, however over the past decade targeted pharmaceutical options have become available for the treatment of PAH. There are different classes of medications available with different mechanisms of actions all which net a vasodilatory and anti-proliferative effect. These medications provide improvement in exercise tolerance, pulmonary hemodynamics and quality of life. This review will attempt to outline all the current treatment options for subject with PAH including new drugs that are on the horizon as based on newly published European Respiratory Society (ERS) and European Society of Cardiology (ESC) guidelines on the diagnosis and treatment of pulmonary hypertension [3].

Classification and diagnosis

Pulmonary hypertension (PHTN) is defined hemodynamically as a mean resting pulmonary

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Table 1. World Health Organization's Classification of Pulmonary Hypertension — Nice [modified from 2]

Group I — Pulmonary arterial hypertension
Idiopathic PAH
Heritable (BMPR2, ALK1, Endoglin, Unknown)
Familial disorder
Related conditions
Collagen vascular disease (Scleroderma)
Congenital systemic-to-pulmonary shunt
Portal hypertension
Human immunodeficiency virus infection
Schistosomiasis
Drugs and toxins (Aminorex ,Fenfluramine ,Dexfenfluramine)
Pulmonary veno-occlusive disease
Persistent pulmonary hypertension of the newborn
Group II — Pulmonary venous hypertension
Systolic dysfunction
Diastolic dysfunction
Valvular disease
Group III — Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitudes
Neonatal lung disease
Group IV — Pulmonary hypertension resulting from chronic thrombotic and/or embolic disease (CTEPH)
Group V — Pulmonary hypertension with unclear multifactorial mechanisms
Hematologic diseases: myeloproliferative disease, splenectomy
Systemic diseases: sarcoidosis, Langerhans cell histiocytosis: neurofibromatosis, vasculitis
Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid diseases

artery pressure (mPAP) greater than or equal 25 mm Hg. The World Health Organization (WHO) has proposed a classification system for pulmonary hypertension based on common clinical features and etiology which has been outlined in Table 1 [2]. Pre-capillary pulmonary hypertension which encompasses pulmonary arterial hypertension (PAH) (WHO Group I), PHTN due to primary lung disease (WHO Group III), Chronic Thromboembolic PHTN (WHO Group IV) and PHTN with an unclear or multifactorial etiology (WHO Group V), is defined as a mPAP greater than or equally to 25 mm Hg as well as a pulmonary artery wedge pressure (PAWP) less than or equal to 15 mm Hg which must be confirmed by right heart catheterization (RHC) [3]. Pulmonary vascular resistance (PVR) has also been added to the definition of PAH. Definitions of PHTN, PAH and subgroups of PHTN have been outlined in Table 2 [3].

Pharmacological management

Once the establishment of a diagnosis of PAH is confirmed via RHC, therapeutic options may be a possibility based on an algorithm (Fig. 1) and PAH disease risk stratification outlines in Table 3. In PAH, the pulmonary vasculature is the exclusive target of disease. The pathologic vasoconstriction and inflammatory vascular remodeling associated with PAH is a prominent feature leading to the rationale for using pulmonary vasodilators therapies and now options are many. The pathophysiology of PAH lies within endothelial dysfunction which leads to an imbalance of vasodilator and vasoconstrictor mediators ultimately resulting in vasoconstriction. In addition dysfunction of the endothelium leads to release of pro-inflammatory mediators. The elucidation of molecules involved in the regulation of pulmonary vasculature has led to the development of currently approved PAH therapies, which all target one of the following key pathways: (1) prostacyclin (PGI2), (2) nitric oxide (NO), and (3) endothelin-1 (ET-1) pathways shown in Figure 2.

Treatment goals in the setting of PAH are focused on the improvement of both hemodynamic parameters and exercise tolerance, resulting in increased survival. Commonly evaluated parameters include: WHO functional class (FC), hemodynamic parameters, mainly right atrial pressure, cardiac index and mixed venous oxy-

Table 2. Hemodynamic definitions of pulmonary hypertension [3]

Definition	Hemodynamics	Clinical Subgroup
Pulmonary Hypertension (PHTN)	mPAP ≥ 25 mm Hg	All types of PHTN
Pre-capillary PHTN	mPAP ≥ 25 mm Hg PCWP ≤ 15 mm Hg	WHO Group I — Pulmonary arterial hypertension WHO Group III — PHTN due to lung disease WHO Group IV — Chronic thromboembolic PHTN WHO Group V — PHTN due to unclear and/or multifactorial etiology
Post-capillary PHTN	mPAP ≥ 25 mm Hg PCWP > 15 mm Hg	WHO Group II — PHTN due to left heart disease WHO Group V — PHTN due to unclear and/ /or multifactorial etiology
Isolated post-capillary PHTN	DPG < 7 mm Hg and/or PVR ≤ 3 WU	
Combined post-capillary and pre-capillary PHTN	DPG ≥ 7 mm Hg and/or PVR > 3 WU	

mPAP — mean pulmonary arterial pressure; PCWP — pulmonary capillary wedge pressure; DPG — diastolic pressure gradient (diastolic PAP — mean PCWP); PVR — pulmonary vascular resistance; WU — wood units

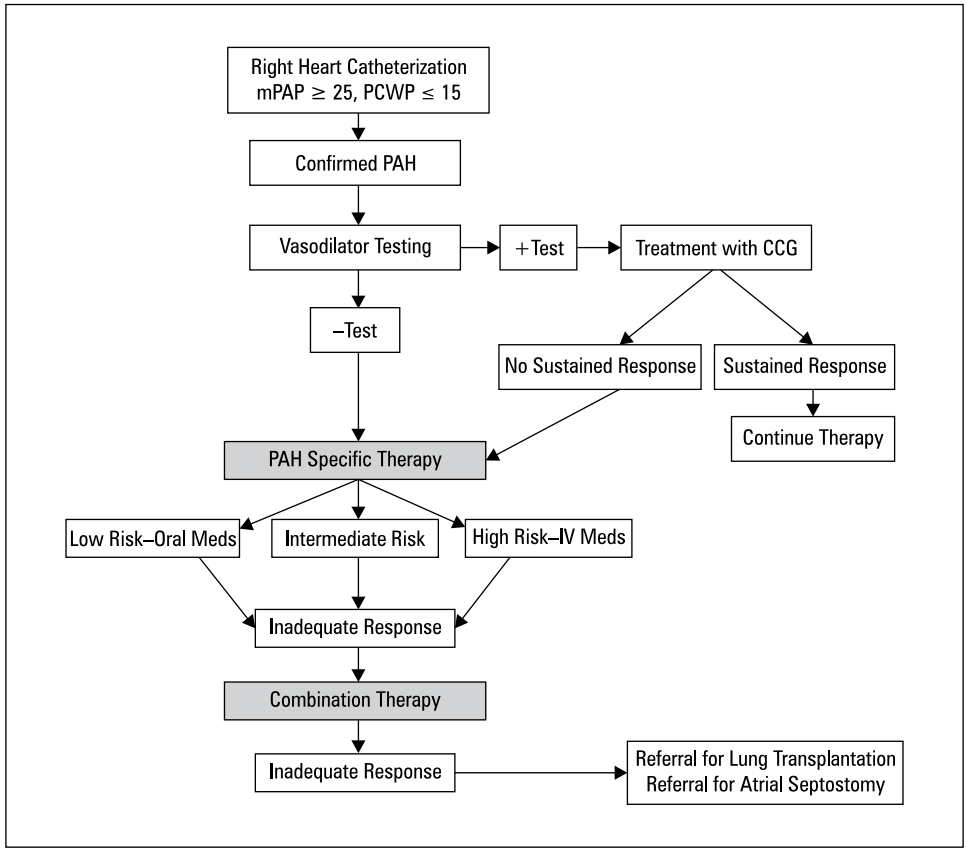


Figure 1. Treatment algorithm for pulmonary arterial hypertension patients; CCG — calcium channel blockers

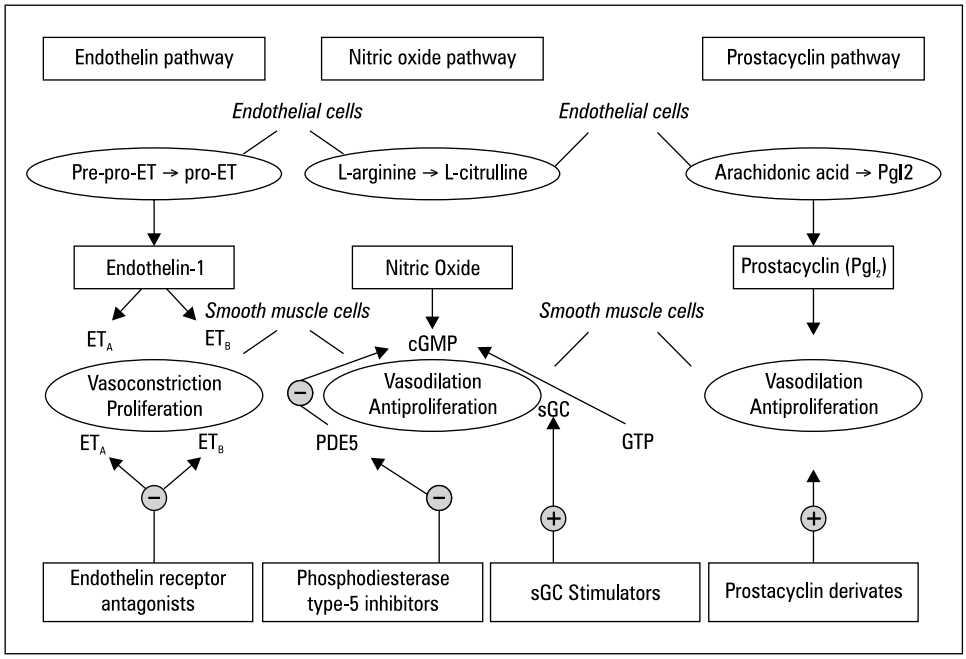
gen saturation, right atrial area and pericardial effusion presence on echocardiography, distance covered on 6 minute walk test (6MWT), peak VO_2 on cardiopulmonary exercise testing and B-type natriuretic peptide (BNP) levels. Goals of PAH therapy have been outlined in Table 4 [4].

The following section will serve to outline general measures and pharmaceutical options that exist in the treatment of PAH. The European Respiratory Society has put forth Classes of Recommendation as well as Levels of Evidence to determine what therapies are most efficacious based on evidence in the literature which have been reflected in the presented tables [3]. Classes of recommendations are as follows: Class I: Evidence and/or general agreement that a given

Table 3. Risk Stratification of PAH Patients based on ERS Guidelines [3]

Clinical Determinant	Low Risk	Intermediate Risk	High Risk
Clinical signs of right heart failure	No	No	Yes
Symptom progression	No	Gradual	Rapid
Syncope	No	Occasional	Repeated
WHO functional class	I, II	III	IV
6MWD	> 440 m	165–440 m	< 165 m
NT-proBNP Plasma levels	BNP < 50 ng/l NT-proBNP < 300 ng/ml	BNP 50–300 ng/l BT-proBNP 300–1400 ng/l	BNP > 300 ng/l BT-proBNP > 1400 ng/l
CPET peak VO^2	Peak VO2 > 15 ml/min/kg	Peak VO2 11–15 ml/min/kg	Peak VO2 < 1 ml/min/kg
Echocardiography Findings	RA are < 18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal pericardial effusion	RA are > 26 cm2 Pericardial effusion
Hemodynamics	RAP < 8 mm Hg CI ≥ 2.5 l/min/m^2	RAP 8–14 mm Hg CI 2.0–2.4 l/min/m^2	RAP > 14 mm Hg CI < 2.0 l/min/m^2

6MWD — 6-minute walk distance; BNP — brain natriuretic peptide; CI — cardiac index; NT-proBNP – n-terminal brain natriuretic peptide; RA — right atrium; RAP — right atrium pressure; VO_2 — oxygen consumption



cAMP — cyclic adenosine monophosphate; cGMP — cyclic guanosine monophosphate; ET — endothelin receptor; GTP — guanosine triphosphate; PDE5 — cGMP -specific phosphodiesterase type 5; PgI2 — prostacyclin; sGC — soluble guanylate cyclase

Figure 2. Mechanism of action and rationale of approved PAH therapies

treatment or procedure is beneficial, useful and effective; Class II: Conflicting evidence and/or a divergence of opinion about the given favor of usefulness/efficacy of the given treatment or procedure: Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy; Class IIb: Usefulness/efficacy is less well established by evidence/opinion; Class III: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. Levels of evidence are as follows: Level of evidence A: Data derived from multiple randomized clinical trials or meta-analysis; Level of evidence B: Data derived from a single randomized trial or large non-randomized studies; Level of evidence C: Consensus of opinion of the experts and/ or small studies, retrospective studies, registries [3].

General measures and non-specific therapies

General measures can be applied to all patients found to have PAH; Recommendations set

Table 4. Goals of PAH specific therapy (adapted from [4])

Functional class	I or II
Echocardiography/cardiac magnetic resonance	normal/near normal RV size and function
Hemodynamics	RAP, 8 mm Hg; CI 2.5 to 3.0 L/min/m^2
6-min walk distance	> 330 to 440 meters may not be aggressive enough in young individuals
Cardiopulmonary exercise testing	Peak VO_2 > 15 ml/min/kg ; $EQCO_2$ <45 l/min/l/min
B-type natriuretic peptide level	normal

CI — cardiac index; RAP — right atrial pressure; RV — right ventricle

Table 5. Recommendations for General Measures [3]

Recommendations	Class	Level
Pregnancy is contraindicated in PAH	I	C
PAH patients should be immunized against influenza and pneumococcal infection	I	C
Psychosocial support is recommended in PAH patients	I	C
Supervised exercise training should be considered in PAH therapy under medical therapy	IIa	B
In elective surgery, epidural rather than general anesthesia should be used	IIa	C
Excessive physical activity that leads to distressing symptoms should be avoided in PAH patients	III	C

Table 6. Recommendations for Supportive Pharmacotherapy [3]

Recommendations	Class	Level
Continuous long term oxygen therapy is recommended in PAH patients when oxygen press is less than 60 mm Hg	I	C
Diuretic treatment in PAH patients with evidence of right ventricular failure and fluid retention	I	C
Oral anticoagulant use in patients with idiopathic or heritable PAH and PAH due to anorexigen use	IIb	C
Correction of anemia and/or iron status in PAH patients	IIb	C

forth by the ERS have been outlined in Table 5. In addition to above-mentioned supportive measures, some pharmacotherapy may be used in conjunction with PAH specific therapies. Continuous long-term oxygen therapy should be initiated in patients who are not able to maintain adequate oxygen saturation (PaO_2 less than 60 mm Hg) [5]. In general patients found to have PAH should adhere to a low sodium diet to avoid volume overload and the careful use of diuretics can be helpful in reducing volume and right heart strain [6]. Care should be taken to avoid excessive diuresis to avoid reduction of cardiac output. It has also been suggested that PAH patients are at risk for in situ thrombosis of altered pulmonary vessels which may contribute to disease progression and it has been proposed that therapeutic anticoagulation might have beneficial effects [7]. Recently concluded COMPERA registry has provided further proof of survival advantage for patients with idiopathic PAH, heritable PAH and drug induced PAH treated with anticoagulants, suggesting that these patients benefit from therapeutic anticoagulation. The situation remains inconclusive for patients with other forms of PAH for whom no therapeutic effect of anticoagulation was detectable [8]. In addition a study has shown that correction of anemia or optimization of iron status may be beneficial in the setting of PAH [9]. Recommendations for the use of support pharmacotherapy has been shown in Table 6. After general measures are initiated PAH specific therapies may be initiated which have been described below.

Calcium channel blockers

For a select group of pulmonary hypertension patients, which include only idiopathic PAH, heritable PAH or drug-induced PAH patients, high dose calcium channel blocker (CCB) therapy may

Table 7. Recommendations on the use of Prostacyclin Analogues (adapted from Galie at al. [3])

Treatment		Class and Level of Recommendation						References
		WHO FC II		WHO FC III		WHO FC IV		
Epoprostenol	Intravenous	–	–	I	A	I	A	[14, 15]
Iloprost	Inhaled	–	–	I	B	IIB	C	[21]
	Intravenous*	–	–	IIa	C	IIB	C	[60]
Treprostinil	Subcutaneous	–	–	I	B	IIB	C	[17]
	Inhaled*	–	–	I	B	IIB	C	[18]
	Intravenous	–	–	IIa	C	IIB	C	[19]
	Oral*	–	–	II	B	–	–	[20]
Beraprost*		–	–	IIb	B	–	–	[61]

*Not approved by European Medicine Agency (EMA) at time of ERS Guidelines publication [3]

be an option. To determine if CCBs are a viable option for such patients, pulmonary vasoreactivity testing for identification of patients is recommended at time of RHC [3]. Acute vasoreactivity is performed with the use of inhaled nitric oxide (NO) at 10–20 parts per million (ppm) but i.v. epoprostenol, i.v. adenosine or inhaled iloprost can be used as alternatives. A positive acute response is defined as a reduction of the mean PAP ≥ 10 mm Hg to reach an absolute value of mean PAP ≤ 40 mm Hg with an increased or unchanged CO. Only about 10% of patients with idiopathic PAH will meet these criteria [10, 11]. In patients who show evidence of an acute hemodynamic response to selective vasodilators during RHC, long-term treatment with CBB, administered orally in high dosages, can produce a sustained hemodynamic response and increase survival [12]. Comparison of responders to acute vasoreactivity testing with the remaining PAH patients revealed that they had less severe disease at baseline. During acute vasodilator testing, long-term CCB responders displayed a more pronounced fall in mean PAP and after 7.0 ± 4.1 years, all but 1 long-term CCB responders were alive in NYHA class I or II, with a sustained hemodynamic improvement. In the group of patients who failed on CCB, the 5-year survival rate was 48% [10].

Prostacyclin analogues

Released by the endothelial cells' prostacyclin I2 (PGI2) is a potent pulmonary vasodilator, exerting its effects via adenylate cyclase. The other mechanisms of action are: the inhibition of platelet aggregation and anti-proliferative effect. Epoprostenol is a PGI2 derivative which has been shown to improve exercise capacity, quality of life, hemodynamics and long-term survival in PAH patients [13, 14]. Demonstrative trial of epoprostenol showed that patient with PAH classified as NYHA functional class III or IV were randomized to receive either conventional therapy alone (warfarin, diuretics, oxygen, and oral vasodilators) or conventional therapy and epoprostenol. Patients in the epoprostenol group had functional improvement, 6MWD (362 m at 12 weeks vs. 315 m at base line) and a decrease in mPAP and pulmonary vascular resistance [15]. There exists also a thermostable form of epoprostenol that lessens its burden of use and may improve patient compliance [16].

Treprostinil is a prostacyclin analogue that has also been successful in treating PAH by improving exercise capacity, functional class, hemodynamics and quality of life [17]. It exists in injectable form as well as a continuous subcutaneous infusion. A double-blind, placebo-controlled multicenter trial in PAH showed that exercise tolerance improved (median change of +10 m (−24 to 47 m; 25^{th}–75^{th} percentile) while unchanged in the placebo (median change of 0 m (−44 to 32 m; 25^{th}–75^{th} percentile). It was also seen that, treprostinil significantly improved indices of dyspnea, signs and symptoms of pulmonary hypertension, and hemodynamics [17]. Of note is the fact that there may be site pain at insertion of subcutaneous catheter. Inhaled [18] and intravenous [19] treprostinil are also options for class II and IV patients. More recently an oral form of treprostinil has been approved as a first line therapy for patients exhibiting functional class III symptoms [20].

Inhaled iloprost has also been shown to induce vasodilatation lasting up to 60−120 minutes and has been shown to improve the dyspnea

Table 8. Recommendations on the use of Endothelin Receptor Antagonists (adapted from Galie at al. [3])

Treatment	Class and Level of Recommendation						References
	WHO FC II		WHO FC III		WHO FC IV		
Ambrisentan	I	A	I	A	IIb	C	[25–27]
Bosentan	I	A	I	A	IIb	C	[17, 22–24, 42]
Macitentan	I	B	I	B	IIb	C	[30]

scores and hemodynamic variables but the major limitation was the repetitive inhalation 6–9 times daily [21]. A randomized, multicenter, placebo-controlled trial involving patients from WHO function class III or IV with PAH 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 [21]. Seventeen percent of treated patients reached this end point, as compared with 4 percent of the placebo group. There was a gain of 59 m on 6MWD among patients with PAH. 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. Recommendations have been presented in Table 8.

Endothelin pathway (endothelin receptor antagonists (ERA))

Endothelin1 (ET-1) is a potent vasoconstrictor and increased levels of ET-1 in vascular endothelial cells and in plasma has been demonstrated in patients with PAH which serves as the rationale for the ERAs. Bosentan was the first ERA approved by the Food and Drug Administration (FDA) for the management of PAH for use in patients with PAH associated with FC II–IV symptoms [22, 23]. Initial studies on WHO Functional Class III scleroderma related PAH patients showed that in the bosentan group 6MWD and cardiac index significantly improved and that pulmonary vascular pulmonary vascular resistance decreased. Patients given bosentan also experienced a reduction of Borg dyspnea index and an improved WHO functional class [24]. Efficacy was further confirmed by the subsequent BREATHE-1 (Bosentan Randomized Trial of Endothelin Antagonist Therapy) trial [17] in which PAH patients who were NYHA functional classes III and IV showed improvement in WHO functional class and the prolongation of time to clinical worsening. Increases in liver aminotransferases greater than 8 times the upper limit of normal were again noted in the bosentan group and were dosage-dependent: with 2 patients in the 125-mg group and 5 patients in the 250-mg group [17]. Bosentan was also studied in NYHA functional class II patients and has demonstrated positive outcomes in this group of patients [23].

Ambrisentan is a highly selective ET-A antagonist with a long half-life to allow once daily dosing that has been approved for PAH functional classes II and III. Data from two studies have shown that ambrisentan taken over 12 weeks significantly improved 6MWD in PAH patients. Associated extension study data also confirmed that continuation of treatment for two years was associated with sustained improvements in exercise capacity and a reduced risk of clinical worsening and death [25]. After demonstrating a favorable safety and efficacy profile in an initial dosing study [26] showing improvement in pulmonary hemodynamics two randomized controlled trials, ARIES-1 and ARIES-2 (ARIES-1, 5 mg, 10 mg, placebo; ARIES-2, 2.5 mg, 5 mg, placebo) were conducted [27]. Both trials showed improvement in 6MWD and in the ARIES-2 trial, there was a significant improvement in time to clinical worsening. Improvement in WHO functional class was found to be significant in the ARIES-1 trial and it was observed in the ARIES-2 trial, but again it was not found to be statistically significant.

Macitentan is the newest Food and Drug Administration (FDA) approved tissue-targeting ERA that has been shown to significantly decrease the risk of a morbidity and mortality event over the treatment period, and improved 6MWD and NYHA FC [28]. Macitentan is a tissue targeting endothelin receptor blocker that inhibits binding of ET-1 to receptors ET-A and ET-B that has been FDA approved for NYHA Class II-III pulmonary arterial hypertension. Macitentan is a lipophilic sulfamide compound designed to decrease vascular resistance by exhibiting enhanced tissue penetration and prolonged receptor binding to ET-A/ET-B in pulmonary arterial smooth muscle cells [29].

A long term randomized, controlled study (SERAPHIN) was conducted. The study was intended to determine safety and efficacy of

macitentan until the first sign of clinical worsening and all-cause mortality in patients with symptomatic pulmonary arterial hypertension. Patients were on Macitentan therapy up to 42 months and a total of 250 patients were randomly assigned to placebo, 250 patients to macitentan 3 mg once-daily, and 242 to macitentan 10 mg daily. Macitentan, at both the 3 mg and 10 mg doses met primary endpoints, decreasing the risk of a morbidity/mortality over the treatment period versus placebo [30].

This risk was found to be reduced by 45% in the 10 mg dose group ($p < 0.0001$) and the 3 mg group showed a risk reduction of 30% ($p = 0.01$). Secondary endpoints included 6MWD change in the first 6 months of therapy as well as NYHA functional class and time to either death or hospitalization due to PAH. These endpoints also showed a dose dependent effect ($p < 0.05$ for either dose) [30].

Adverse events and discontinuation of treatment due to adverse events was similar across all groups. Adverse events associated with macitentan were headache, nasopharyngitis, and anemia. Elevations of liver aminotransferases greater than three times the upper limit of normal were observed in 4.5% of patients receiving placebo, in 3.6% of patients on 3 mg of macitentan and in 3.4% of patients on 10 mg of macitentan [30]. Recommendations have been presented in Table 8.

Nitric Oxide Pathway (Phosphodiesterase 5 Inhibitors)

Nitric Oxide (NO) is a short acting endogenous molecule that plays a key role for controlling vascular smooth muscle tone that results in vasodilatation and inhibiting proliferation. NO diffuses through cells and activates soluble guanylate cyclase leading to an increase in cyclic guanosine 3'−5' monophosphate (cGMP) resulting in smooth muscle relaxation. The enzyme PDE-5 inhibitors are abundantly expressed in high concentration in the lungs, platelets and vascular smooth muscle and are responsible for degradation of cGMP [31].

At the level of the endothelium nitric oxide indirectly acts as a potent vasodilator by upregulating the production of cyclic guanosine monophosphate (cGMP). Phosphodiesterase type 5 (PDE-5) is an enzyme that degrades cGMP leading to vasoconstriction [31]. Sildenafil, the first PDE-5 inhibitor approved for PAH is indicated for patients with FC II-III symptoms. Patients that are on this medication have shown improvement in symptoms, 6MWD as well as FC [26]. Clinical research studies have found sildenafil to improve pulmonary hemodynamic and exercise capacity in PAH patients.

Initially a double blinded, placebo-controlled, cross over study of 22 patients randomized to receive sildenafil or placebo for 6 weeks and then crossed over with a primary endpoint of exercise tolerance demonstrated clinical efficacy [32]. Patients on sildenafil showed significant improvement in exercise time while the placebo arm showed a decrease in exercise tolerance. Other improvements noted were cardiac index assessed by echocardiography along with dyspnea and fatigue components of QoL, however no significant improvement was seen in estimated pulmonary artery systolic pressure (PASP) [32].

The trial that demonstrated clinical efficacy of sildenafil was the SUPER-1 trial [33]. The SUPER-1 trial was a double blind, multi- center, placebo controlled study of 278 PAH patients. PAH symptomatology was either idiopathic, associated with connective tissue disease or with repaired congenital systemic to pulmonary shunts. Most patients belonged to WHO functional class II (39% of patients) or III (58% of patients). Patients were randomized to receive placebo or sildenafil 20 mg, 40 mg or 80 mg three times daily for 12 weeks. The primary endpoint of the study was to monitor for change in distance walked in 6 minutes from baseline to 12 weeks. By the end of 12 weeks, there was significant improvement in walk distance of 45 m, 46 m and 50 m in all three dose regimens of 20 mg, 40 mg and 80 mg, respectively. Sildenafil was found to improve exercise capacity in all three groups over placebo. The study also noted a significant improvement in hemodynamic measurements such as mPAP, cardiac index and PVR. There was also improvement change in functional class, with no significant delay in time to clinical worsening or Borg Dyspnea Index (BDI) [33].

Tadalafil is the second PDE-5 inhibitor to be approved for PAH WHO Group 1 patients. The first large scale trial to study the efficacy of Tadalafil was the PHIRST study [34]. The study was a 16 weeks double blinded, placebo controlled and multi-centered study of 405 patients (WHO Group 1, FC II or III) who were either on bosentan or one of five treatment arms. Patients were randomized into once daily dosing of 2.5 mg, 10 mg, 20 mg, 40 mg or a placebo group. The primary endpoint of study was to detect any change in 6MWD from baseline. Along with 6MWD, secondary endpoints measured were WHO FC, hemodynamic changes, Borg dyspnea scale and quality of life. It was fo-

Table 9. Recommendations on the use of Phosphodiesterase 5 Inhibitors (adapted from Galie at al. [3])

Treatment	Class and Level of Recommendation						References
	WHO FC II		WHO FC III		WHO FC IV		
Sildenafil	I	A	I	A	IIb	C	[32, 33]
Tadalafil	I	B	I	B	IIb	C	[34]
Vardenafil*	IIb	B	IIb	B	IIb	C	[51]

*Not approved by European Medicine Agency (EMA) at time of ERS Guidelines publication [3]

und the tadalafil group showed an improvement in 6MWD. There was also reduced incidence of clinical worsening, fewer hospitalizations and showed significant improvement, in health related QoL, No improvement was observed in Borg dyspnea score or WHO classification for any given treatment arm, which was a consistent finding with other studies as well. Recommendations have been presented in Table 9.

Soluble guanylate cyclase (sGC) stimulator

Riociguat is a direct sGC stimulator that is the only therapy approved by the Food and Drug Administration. Riociguat stabilizes NO-soluble guanylate cyclase coupling and directly stimulates soluble guanylate cyclase, increasing the production of cyclic guanosine monophosphate (cGMP) and causing vasodilation [35]. In addition it acts in synergy with NO to produce anti-aggregatory, anti-proliferative and vasodilatory effects [36, 37] by increasing the concentrations of cGMP.

The PATENT-1 Trial was a phase 3, double blinded study that riociguat improved the 6-minute walk distance both in naïve patients and patents who were also on in those who were receiving ERAs or prostanoids (+30 m in the 2.5 mg-maximum group and had decreased by a mean of 6 m in the placebo group (least-squares mean difference, 36 m; 95% confidence interval, 20 to 52; $P < 0.001$). There were significant improvements in pulmonary vascular resistance, NT-proBNP levels, WHO functional class, time to clinical worsening, and Borg dyspnea score [38]. Generally riociguat is well tolerated with the most common side effects are headache and dizziness which has been seen in up to one quarter of patients. Other common side effects include upset stomach, leg swelling, runny nose and nausea. Syncope was only seen one percent of patients. It is important to note that riociguat is metabolized thought the cytochrome p450 pathway, most specifically CYP1A1. For these reason patients who smoke may require increased dosages due to fact that CYP1A1 is inducible by chemicals found in cigarette smoke [39]. In addition riociguat is the only drug that has been approved for the treatment of WHO Group IV chronic thromboembolic pulmonary hypertension (CTEPH) [40]. For the treatment of WHO FC II and III, the ERS guidelines give a IB Class-Level recommendation and for WHO FC IV patients a IIb-C recommendation [3].

Combination therapy

With the presence of multiple pathways at play in the treat of PAH, the possibility to use a more than one medication exists. It is known that up to 36% of patients receive combinations therapy and up to 9% receive triple therapy [41]. Initially it was the BREATHE-2 study, a randomized controlled trial that evaluated initial combination which failed to demonstrate any significant advantage of initial combination of epoprostenol and bosentan compared with epoprostenol alone [42]. More recently though the AMBITION trial, in which initial therapy with tadalafil and ambrisentan was found to be superior to monotherapy and showed a 50% risk reduction in clinical worsening and well as increased 6MWD and PAH related hospitalizations [43]. However it is still unclear if upfront combination therapy improves long-term outcomes in comparison to sequential add-on therapy in case of poor response to monotherapy. Recommendations have been outlined in Table 10.

After initialization of PAH specific therapy patients are reassesses in 3–6 months. Certain parameters are taken into account to see if the patient is responding to initiated medication. Clinical response is based on patients overall feeling, WHO functional class, exercise capacity, estimated echocardiogram pressures, 6MWD amongst others. If clinical response is found to be inadequate then addition of a second or tertiary medication may be warranted. Meta-analysis of data shows that combination therapy is beneficial to patients [44]. Multiple studies have addressed add-on combination therapy such as the STEP

Table 10. Recommendations on the use Combination Therapy in PAH (adapted from Galie at al. [3])

Combination Therapy	Class and Level of Recommendation						References
	WHO FC II		WHO FC III		WHO FC IV		
Ambrisentan + tadalafil	I	B	I	B	IIb	C	[43]
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C	–
Bosentan + sildenafil + epoprostenol	–	–	IIa	C	IIa	C	[62]
Bosentan + epoprostenol	–	–	IIa	C	IIa	C	[63]

ERA — endothelin receptor antagonists; PDE-5i — phosphodiesterase 5 Inhibitors

Table 11. Recommendations on the use sequential Combination Therapy in PAH according to WHO FC (adapted from Galie at al. [3])

Combination Therapy	Class and Level of Recommendation						References
	WHO FC II		WHO FC III		WHO FC IV		
Macitentan added to sildenafil	I	B	I	B	IIa	C	[30]
Riociguat added to bosentan	I	B	I	B	IIa	C	[38]
Selexipag* added to ERA and/or PDE-5i	I	B	I	B	IIa	C	[49, 50]
Sildenafil added to epoprostenol	–	–	I	B	IIa	B	[64]
Inhaled treprostinil added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C	[18]
Inhaled iloprost added to bosentan	IIb	B	IIb	B	IIb	C	[45]
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C	[34]
Ambrisentan added to sildenafil	IIb	C	IIb	C	IIb	C	[65]
Bosentan added to epoprostenol	–	–	IIb	C	IIb	C	[66]
Bosentan added to sildenafil	IIb	C	IIb	C	IIB	C	[67, 68]
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C	[68]
Other double/triple combination	IIb	C	IIb	C	IIb	C	–
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B	[48]

*Not approved by European Medicine Agency (EMA) at time of ERS Guidelines publication [3]; ERA — endothelin receptor antagonist; PDE-5i — phosphodiesterase 5 inhibitors

study in which inhaled iloprost was added to patients already on bosentan. Though a small sample size, results of this study demonstrate that the addition of inhaled iloprost in patients with PAH with reduced exercise capacity on bosentan monotherapy is safe and efficacious (+26 m on 6MWT) [45]. Similarly The TRIUMP I study showed that PAH patients who remain symptomatic on bosentan or sildenafil, the addition of inhaled treprostinil improves exercise capacity and quality of life and is safe and well-tolerated [18]. As for other trials, it has been seen that the addition of the ERA macitentan to pretreated patients significantly delayed PAH related events [30] and that addition of bosentan to sildenafil n the COMPASS-2 trial improved exercise capacity at week 16 but did not meet other primary endpoints [46]. The recommendations on efficacy of sequential combination therapy set worth by the ERS have been outlined in Table 11.

Drug interactions

With the majority of patient with severe PAH being placed on combination therapy and evidence pointing towards initial combination therapy, the use of multiple drugs working on multiple pathways creates the possibility of drug-drug interactions and should be considered by physicians when prescribing PAH specific therapy.

Clinicians must take some considerations even in the setting of monotherapy. The PDE-5 sildenafil is metabolized via the cytochrome P450 pathway specifically involving CYP3A4 and CYP2C9. There is an increase in sildenafil bioavailability and reduced clearance with CYP3A4 substrates and inhibitors and CYP3A4 substrates

Table 12. Potential Interactions Between Pulmonary Arterial Hypertension-specific Medications for Concurrent Illnesses

	Statins	Sulph.	RTIs	Protease Inhibitors	Af	Cyclos.	Hormonal Contraceptives
Prostacyclin Analogues							
Epoprostenol	–	–	–	–	–	–	–
Treprostinil	–	–	–	–	–	–	–
Iloprost	–	–	–	–	–	–	–
Phosphodiesterase Type 5 Inhibitors							
Sildenafil	–	X	–	X	X	–	–
Tadalafil	–	X	–	X	X	–	–
Soluble Guanylate Cyclase Stimulators							
Riociguat	X	X	–	X	X	X	–
Endothelin Receptor Antagonists							
Bosentan	X	X	X	X	X	X	X
Ambrisentan	–	–	–	X	–	X	–
Macitentan	–	–	–	X	–	X	–

All data was obtained from FDA Drug Information Data; RTI — reverse transcriptase inhibitor; X — known interaction; – — no known interaction or not clinically significant interaction; Cyclos — cyclosporine A; Barb — barbituates; Af — antifungals

plus beta-adrenoceptor blockers. Drugs that are CYP3A4 inducers such as barbiturates, rifampicin and St John's wort may lower sildenafil levels and should be used with caution. Sildenafil levels are modestly increased by fresh grapefruit juice, a weak inhibitor of CYP3A4 [3].

The ERA bosentan is an inducer of cytochrome P450 isoenzymes CYP3A4 and CYP2C9. Plasma concentrations of drugs metabolized by these isoenzymes will be reduced when co-administered with bosentan. Of note is that the combination of a potent CYP3A4 inhibitor (ketoconazole, ritonavir) and/or a CYP2C9 inhibitor (e.g. amiodarone, fluconazole) with bosentan may cause a significant increase in plasma bosentan levels and thus is contraindicated. Interactions may theoretically occur with certain antifungals as well as immunosuppressive drugs. An outline of PAH specific medications and interactions with commonly used drugs is shown in Table 12.

Now with PAH specific combination therapy becoming commonplace there are a few important therapeutic combinations that should be avoided. The use of ERA bosentan with PDE-5 sildenafil has been shown to significantly decrease plasma concentrations of sildenafil [47]. In addition the PATENT PLUS trial studied the effect of adding the soluble guanylate cyclase stimulator, riociguat to background sildenafil therapy which concluded that riociguat in combination with sildenafil was associated with high rates of discontinuation due to hypotension, SAEs and deaths [48]. Therefore concomitant use of riociguat with PDE-5 inhibitors (such as sildenafil, tadalafil and vardenafil) is contraindicated. Common dosing of medications has been presented in Table 13.

Future medications

As the vascular wall remain the primary target in PAH specific drugs, new medications focus on these biological pathways. The majority of current therapeutic research is focused on the prostacyclin and nitric oxide pathways. Selexipag is an oral, selective prostacyclin receptor agonist which is currently awaiting approval of the FDA. In a proof of concept study by Simonneau et al. it has been found that Selexipag use in patients already receiving ERA or PDE-5 therapy, resulted in a 30.3% reduction in mean pulmonary vascular resistance versus placebo and systemic vascular resistance along with an increase in cardiac index [49]. The formal results of the GRIPHON study, a multicenter, double blinded, placebo controlled phase 3 study of 1156 show that selexipag reduced the risk of mortality/morbidity events vs. placebo by 40% and the treatment effect was consistent across age, gender, etiology, baseline FC and background PAH therapy sub-groups [50]. Though not yet approved by the EMA based on the ERS guidelines a Class-Level recommendation

Table 13. Pulmonary Arterial Hypertension Medications Dosing

Medication Class and typical drug dosing range	Adverse Effects
Phosphodiesterase Type-5 Inhibitors	
Sildenafil Oral: 5mg or 20 mg three times daily; separate dosing by 4–6 hrs IV: 2.5-mg or 10-mg bolus three times daily	Epistaxis, headache, dyspepsia, flushing, insomnia, erythema, dyspnea worsened, rhinitis, sinusitis, myalgia, pyrexia, paresthesia; hypotension, vision or hearing loss, priapism, vaso-occlusive crisis
Tadalafil 40 mg once daily. CrCl 31–80 ml/min: initially 20mg once daily, increase to 40 mg once daily if tolerated. CrCl < 30 ml/min: not recommended	Headache, myalgia, nasopharyngitis, flushing, respiratory tract infection, pain, nausea, dyspepsia, sinus congestion; hypotension, sudden vision or hearing loss, priapism, prolonged erection
Soluble Guanylate Cyclase (sGC) Stimulator	
Riociguat 0.5—2.5 mg daily in three divided	Hypotension (low blood pressure), headache, and gastrointestinal disorders
Endothelin Receptor Antagonists	
Ambrisentan 5—10 mg daily	Peripheral edema, nasal congestion, sinusitis, flushing, elevated liver enzymes; decreased sperm counts, hematologic changes
Bosentan < 40 kg: 62.5 mg twice daily. > 40 kg: Initially 62.5 mg twice daily for 4 weeks, then 125 mg twice daily. Take in the AM and PM	Hepatotoxicity, respiratory tract infection, headache, edema, chest pain, syncope, flushing, hypotension, sinusitis, arthralgia, elevated liver enzymes, palpitations, anemia; decreased sperm counts
Macitentan 10 mg once daily	Hepatotoxicity, Anemia, lightheadedness, headache, urinary tract infection
Prostacyclin Analogues	
Treprostinil IV/SQ: 1—10 mg/ml for infusion. Oral — 0.125 mg, 0.25 mg, 1 mg, 2.5 mg twice daily, titrating up. Inhaled — 1.74 mg in 2.9 ml inhalation. 3 breaths of treprostinil per treatment session, 4 times daily	Infusion reactions/site pain, headache, diarrhea, nausea, jaw pain, vasodilatation, dizziness, edema, pruritus, hypotension
Epoprostenol IV: 2 nanograms/kg per min; increase in increments of 2 nanograms/kg per min at ≥ 15 minute intervals until response achieved or tolerance develops	Headache, jaw pain, flushing, GI upset, flu-like symptoms, anxiety, dizziness, tachycardia, myalgia
Iloprost 10 mcg/ml, 20 mcg/ml; soln for inhalation using I-neb six to nine times daily (no more than every 2 hours) IV: 1 mg/ml for infusion	Vasodilation, increased cough, headache, lockjaw, insomnia, GI upset, hypotension, flu syndrome, back pain, increased GGT, alkaline phosphatase, tongue pain, palpitations, syncope, muscle cramps, hemoptysis, pneumonia, CHF, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, kidney failure

*All data was obtained from FDA Drug Information Data

of I-B has been given for both WHO FC II and III patients [3].

Another drug under investigation is Vardenafil, which is considered a PDE-5 inhibitor. It differs from already marketed PDE-5 inhibitors by having a short effective time and slight longer half life than that of sildenafil. The EVALUATION study by Jing et al., which sought out to demonstrate safety and efficacy of Vardenafil showed that it is well tolerated in twice daily dosing and showed a increase in 6MWD, and cardiac index, along with an decrease in mean pulmonary arterial pressure and pulmonary vascular resistance [51]. Though not yet approved by the EMA based on the ERS guidelines a Class-Level recommendation of IIbB has been given for both WHO FC II and III patients and a recommendation of IIb-C for WHO FC IV patients [3].

In addition to traditional pathways a new class of drug exists. Bardoxolone methyl is an Nrf2 activator and NF-κB suppressor that targets dysfunctional inflammatory, metabolic, and bioenergetic pathways and is thought to have beneficial effects on endothelial dysfunction, as well as anti-proliferative and anti-fibrotic effects [52]. The LARIAT trail is a phase 2, dose-ranging, randomized, placebo-controlled, double-blind trial to assess exercise capacity and safety in patients taking stable PAH background therapy. Initial results showed bardoxolone methyl significantly increased placebo-corrected 6MWD in PAH patients on background oral

PAH therapies and was well-tolerated at doses up to 10 mg [53].

There have also been exploratory studies into three pathways different than the ones mentioned above with unsatisfactory results using the following compounds: inhaled vasoactive intestinal peptide, tyrosine kinase inhibitors (platelet-derived growth factor inhibitors) and serotonin antagonists [3]. These drug compounds should be avoided.

Non pharmacological considerations

As there is presently no cure for PAH, in addition to these pharmaceutical options, supervised exercise training should be considered [54]. It has been shown to increase exercise capacity, WHO functional class, peak oxygen consumption and resting heart rate [55, 56]. It has also been observed that exercise may improve health related quality of life (HRQoL) [30], depression and fatigue [57] which are all important in the overall well being of the patient. Nevertheless excessive physical activity leading to distressing symptoms is not recommended in PAH patients.

PAH specific therapy has reduced and delayed patient referral for lung transplant but it remains an important option for non-responders to therapy [58]. The outcome of medically treated patients is not always clear. Lung transplantation should continue to be an important option for those who fail on PAH specific therapy and remain in WHO-FC III or IV as it is for patients who have PHTN in the setting of interstitial lung disease [59].

Conclusion

Pulmonary arterial hypertension (PAH) is a rare and devastating disease due to direct injury to the pulmonary vessels and vascular bed. At present there is no cure for PAH, however targeted pharmaceutical options have become available for the treatment of PAH. There are different classes of medications available with different mechanisms of actions all which net a vasodilatory effect. After definitive diagnosis is made via right heart catheterization proper therapeutic options should be explored depending on patients' concurrent medication and medical conditions.

Conflict of interest

The authors declare no conflict of interest.

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