TABLE 304-2 FDA-APPROVED THERAPIES FOR THE TREATMENT OF PAH

Generic Name	Route of Administration	Drug Class	Indication
Epoprostenol	IV	Prostacyclin derivative	Treatment of PAH to improve exercise capacity
Iloprost	Inhaled	Prostacyclin derivative	Treatment of PAH to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration
Treprostinil	IV or SC	Prostacyclin derivative	Treatment of PAH to diminish symptoms associated with exercise
Treprostinil	Inhaled	Prostacyclin derivative	Treatment of PAH to improve exercise ability
Treprostinil	Oral	Prostacyclin derivative	Treatment of PAH to improve exercise ability
Bosentan	Oral	Non-selective endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and to decrease clinical worsening
Ambrisentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and delay clinical worsening
Macitentan	Oral	Non-selective endothelin antagonist	Treatment of PAH to improve exercise capacity and delay clinical worsening
Sildenafil	Oral	PDE5 inhibitor	Treatment of PAH to improve exercise capacity and delay clinical worsening
Tadalafil	Oral	PDE5 inhibitor	Treatment of PAH to improve exercise ability
Riociguat	Oral	Soluble guanylyl cyclase stimulator	Treatment of PAH to improve exercise capacity and delay clinical worsening

Abbreviations: FDA, U.S. Food and Drug Administration; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDES, phosphodiesterase-5.

The randomized, placebo-controlled, phase III Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE)-1 comparing bosentan with placebo demonstrated improved symptoms, 6MWD, and WHO functional class. The Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients (EARLY) comparing bosentan with placebo demonstrated improved PVR and 6MWD.

Several studies, including the phase III, placebo-controlled Ambrisentan in Pulmonary Arterial Hypertension-1 (ARIES-1) trial, suggest that ambrisentan improves exercise tolerance, WHO functional class, hemodynamics, and quality of life in patients with PAH. There are no trial data to evaluate whether the selective ET-A receptor antagonism of ambrisentan has any advantage over the nonselective ET receptor antagonism of bosentan.

Phosphodiesterase Type-5 Inhibitors Nitric oxide derived from endothelial cells activates guanylyl cyclase, which, in turn, generates cGMP in vascular smooth muscle cells and platelets. cGMP is a second messenger that induces vasodilation through relaxation of the arterial smooth muscle cells and inhibits platelet activation. PDE5 enzymes metabolize cGMP. Therefore, cGMP PDE5 inhibitors prolong the vasodilatory effect of nitric oxide, especially within the pulmonary arterial bed where high concentrations of cGMP are found. There are currently two PDE5 inhibitors used for the treatment of PAH, sildenafil and tadalafil. Both agents have been shown to improve hemodynamics and 6MWD. Recently, the oral soluble guanylyl cyclase stimulator, riociguat, was approved for the treatment of both PAH and CTEPH.

Unmet and Future Research Needs in Pulmonary Hypertension Presently there are only three classes of therapy for patients with PAH, and even with therapy, the median survival for a person with PAH is only 5–6 years (Table 304-2). Although there are five subtypes of PH, current approved therapies only address one subtype. Not only do we need to expand the treatment options for patients with PAH, we also need to develop effective therapies for all patients with PH. Limited survival is, in part, a result of delay in diagnosis. Improved awareness among clinicians and patients could lead to more timely diagnosis that will affect the response to therapy and survival. PH needs to be diagnosed in a timely manner so that therapy can be initiated as soon as possible. Patients should also have the option of referral to a specialty center that focuses on treatment of patients with pulmonary vascular disease, which will ensure their access to state-of-the-art care and a multidisciplinary approach to care. Finally, there need to be continued efforts at developing new therapies that target the increasingly complex and overlapping pathways involved in the various forms of PH.