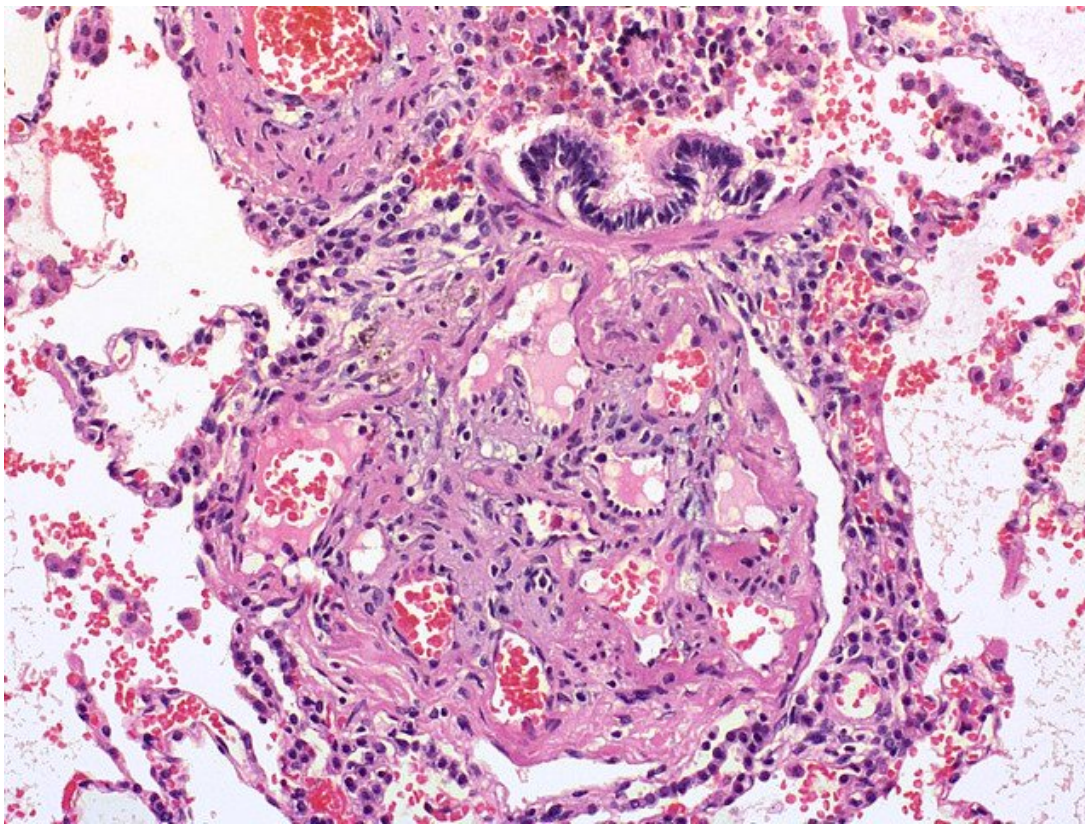


Pulmonary Hypertension Medication: Outline of Pharmacological Therapy

[See online here](#)

In this article, we will be reviewing mainly about the advanced therapies which are available for pulmonary hypertension with the brief coverage of primary therapy. The advanced therapies are especially studied for IPAH.



Introduction and Scope

[Pulmonary hypertension](#) (PH) is the increased pressure inside the vasculature of the [lungs](#), leading to symptomatic manifestations which can be life-threatening in the absence of treatment. There are many causes of pulmonary hypertension and the World Health Organization divides the cause into **5 groups**.

Group 1 is the primary arterial hypertension and consists of idiopathic pulmonary arterial hypertension (IPAH), heritable disorders, connective tissue, and [HIV infection](#). Group 2 includes those due to an overload in the left ventricle, group 3 involves inherent lung diseases, group 4 finally is the thromboembolic formation, and group 5 consists of the miscellaneous causes including [sarcoidosis](#). It is very important to have knowledge of the **classification**, as the **treatment is based upon it**.

There are two types of therapy, first is the **primary therapy**, which is aimed at the underlying condition which is responsible for pulmonary hypertension, and another is the **advanced therapy** which is aimed at symptomatic treatment.

Outline of Pharmacological Treatment

The classes of drugs which are used for the advanced therapy of pulmonary hypertension include:

- **Prostacyclin pathway agonist**
- **Endothelin receptor antagonists**
- **Nitric oxide (NO)-cGMP enhancers**
- **Calcium channel blockers**

Among the agents which are available, there is no single agent which is superior over the other, and the selection of the pharmacological agent is dependent on multiple factors like the right ventricular function, vasoreactivity test, individual physician's discretion, and the functional class to which the person belongs according to the WHO functional class classification of primary hypertension.

Vasoreactivity Testing

Vasoreactivity testing **helps in identifying those patients who would be responding to calcium channel blocker when it is given for treatment.** The test is performed by catheterization of the right heart. This is followed by the administration of short-acting vasodilators like intravenous epoprostenol, intravenous adenosine, and inhaled nitric oxide, and the hemodynamic responses are measured.

The test is stated positively if the primary artery pressure falls down by at least 10 mm Hg without any or minimal effect on cardiac output and systemic blood pressure. The advantages of starting the treatment with [calcium channel blockers](#) like dihydropyridine or diltiazem are that it is relatively cheap when compared to the advanced newer treatments, as it has relatively fewer side effects and is the better-studied agent. Those persons, who were negative to vasoreactivity tests, have to be treated with advanced newer agents as the vasodilator are not expected to improve outcomes in these patients.

WHO Functional Class-Based Treatment

Class 1 usually does not require any treatment pharmacologically. Class 2 and class 3 are generally started with endothelin and nitric oxide-cGMP pathways combination therapy. The class 1 is comfortable in rest, class 2 develops [dyspnea](#) on ordinary activity, class 3 develops dyspnea at less than normal physical activity and class 4 has dyspnea at rest.

Calcium Channel Blockers

Classification and Mechanism of Action

The drugs under this category include long-acting nifedipine, amlodipine, and diltiazem. These are the inhibitors of voltage-gated calcium channels and thus preventing the transmembrane transport of calcium. The decrease in the concentration of the calcium causes vasodilation.

Pros and Cons and the Main Indication of the Group

The drug is especially indicated in those patients who have a **positive vasoreactivity test** (though the evidence available is not very compelling).

Adverse and Side Effects Related to the Group

Flushing (due to nonspecific dilation of the systemic vessels in the face), **peripheral edema, dizzy feeling, giddiness, headache, a sensation of vomiting, atrioventricular block and bradycardia**. The mechanism behind the development of hypotension (due to systemic vasodilation which is produced non-specifically) and ventilation-perfusion mismatch (due to pulmonary vasodilation).

Calcium channel blockers (dihydropyridines)	Calcium channel blockers (non-dihydropyridines)
Nifedipine (Adalat ^R), amlodipine (Norvasc)	Diltiazem (Tiazec ^R), verapamil (Isoptin ^R)
Directly affected Ca channels on the blood vessels	Directly affects Ca channels on the blood vessels and in the heart
Causes reflex tachycardia	Does not cause reflex tachycardia
Side effects <ul style="list-style-type: none">• Constipation (common)• Fatigue (rare)• Edema (5-20%)	Side effects <ul style="list-style-type: none">• Constipation (rare)• Fatigue (common)• Edema (1-5%)
May interact with grapefruit!	May interact with grapefruit!

Prostacyclin Pathway Agonists

Classification and Mechanism of Action

The group of drugs under this category include

- Intravenous Epoprostenol (Prostacyclin)
- Analogs of prostacyclin, which are synthetic in nature like Iloprost, intravenous, subcutaneous Treprostinil and inhaled Treprostinil
- Prostacyclin receptor agonists, which do not have a prostanoid group like Selexipag

Prostacyclin, as a group, is a powerful dilator of the vascular bed and also decreases the platelet aggregation by means of increasing the cyclic adenosine monophosphate (CAMP) concentration. It also prevents the formation of thrombosis by means of the above mechanism.

Pros and Cons and the Main Indication of the Group

Epoprostenol

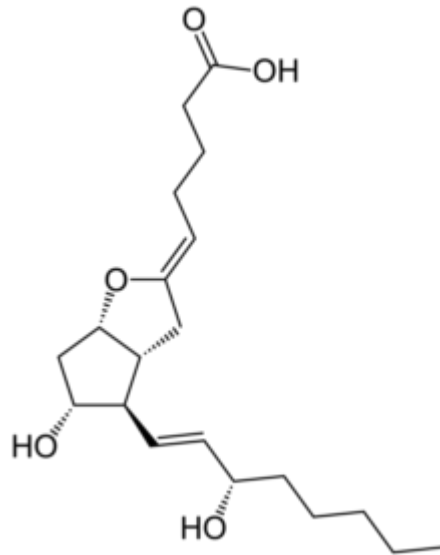


Image: "Epoprostenol". License: Public Domain

The most important drug in this group remains epoprostenol. When this drug is given intravenously to IPAH patients, it **improves the survival capacity, increases the hemodynamic stability and increases the functional capacity**. There are permanently implanted venous catheters to the central line associated with the infusion pump for delivering epoprostenol continuously. This drug is recommended for the treatment of **pregnant women** suffering from class 3 and class 4 pulmonary hypertension.

Treprostinil

Treprostinil is available in an intravenous, subcutaneous and the inhaled route. The offering of the subcutaneous route has the advantage of treprostinil over epoprostenol. The subcutaneous route has the latest concerns of pain at the injection site.

Iloprost

Iloprost can be given in an inhaled route. The advantage of giving an iloprost in this route is that it can act directly over the vasculature of the lungs and can produce the effect. The side effects which are present with intravenous administration of epoprostenol can be avoided, but this comes at a cost of increased frequency of administration around 6 to 9 times a day.

Selexipag

Selexipag have a prostacyclin IP receptor selective agonist activity. The IP receptor is a non-prostanoid receptor, and is different from the mechanism of action of other prostacyclin agonists. In the GRIPHON trial, the drug showed a moderate increase in the survival capacity, along with the reduction in hospitalization and progression of the disease when compared with a placebo.

Adverse and Side Effects Related to the Group

Flushing (due to the dilation of the systemic vessels) can happen, as well as a sensation of vomiting, headache, pain in the joints (arthralgia), jaw pain, falling blood pressure, dizzy feeling, pain in the chest, dermal ulcer, eczema, injection site infection and a nervous feeling.

Endothelin Receptor Antagonist

Classification and Mechanism of Action

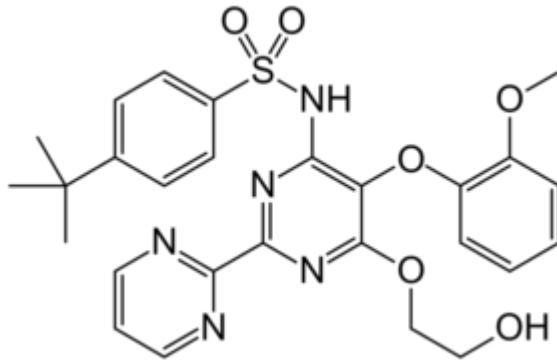


Image: "Structural Diagram of Bosentan" by Fvasconcellos.
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The drugs falling under this category include Bosentan, Macitentan, Ambrisentan and Sitaxsentan. Bosentan and Macitentan are nonspecific endothelin receptor antagonists. Ambrisentan acts specifically on the endothelin type A receptor. The rationale behind using this drug is that endothelin-1 is present in an increased quantity in the lungs in the patients suffering from IPAH, and it is a powerful vasoconstrictor and also causes proliferation of the smooth cells by acting as a mitogen.

Pros and Cons and the Main Indication of the Group

According to a Cochrane review, it was confirmed that Bosentan is associated with an **improvement in the functional capacity, the decrease of symptoms and improvement in the hemodynamic measures**. The drug improves the survival capacity in the case of IPAH.

Adverse and Side Effects Related to the Group

Hepatotoxicity is the main adverse effect of all the endothelin receptor antagonist and Sitaxsentan is withdrawn from the market following fatal cases of hepatotoxicity. This requires monitoring of the hepatic function test in regular intervals. Other adverse effects include **peripheral edema**. This class of drug is contraindicated in pregnant women as it is highly teratogenic. Macitentan has the problem of the development of nasopharyngitis and anemia.

Nitric Oxide CGMP Enhancers

Classification and Mechanism of Action

Sildenafil, Tadalafil, and Vardenafil belong to the group of drugs which act as phosphodiesterase 5 inhibitor. Phosphodiesterase 5 is involved in the breakdown of CGMP, and the inhibition of this enzyme leads to the accumulation of CGMP. This causes dilation of the [blood vessels](#) of the pulmonary vasculature. Vardenafil is awaiting FDA approval and not yet approved for PAH.

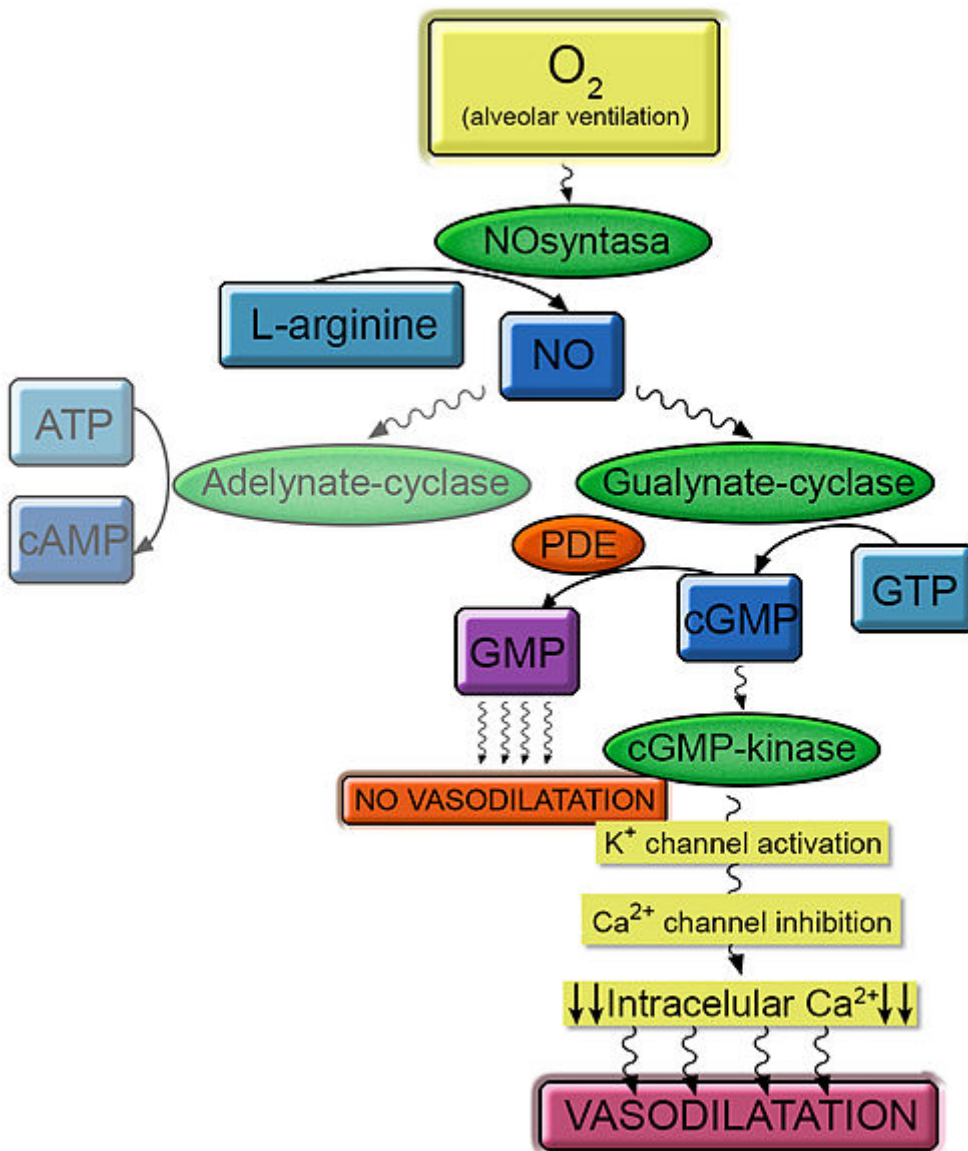


Image: "Molecular Pathway of Vasodilation Mediated by cGMP" by BQmUB2012010. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

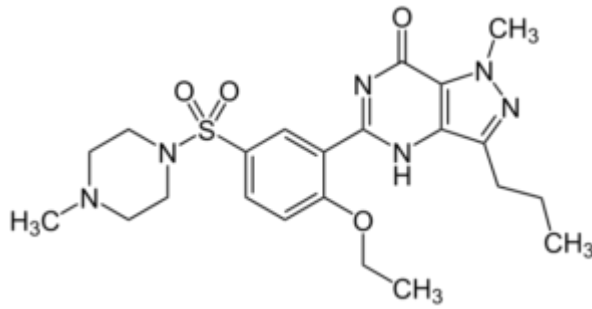
Pros and Cons and the Main Indication of the Group

These groups of drugs have reported an improvement in the functional outcome, and also a decrease in the deterioration seen clinically, but an improvement in the mortality rate has not been fully documented. It should also be known that this group of drugs is used as a treatment of erectile dysfunction, which is one of the common sexual dysfunction seen in males.

Adverse and Side Effects Related to the Group

Flushing, headache, impaired digestion, and disturbances in vision like blurring, color changes (cyanopsia), photophobia, **bleeding and congestion of the nose**. The other side effects include difficulty in sleeping, dizzy feeling, pain and discomfort in the abdomen, elevation of **liver** enzymes and erythema.

Guanylate Cyclase Stimulant



[Image](#): "Sildenafil" by Yikrazuul. License: Public Domain

Riociguat is the drug which falls under this category. It is available in an oral formulation. Guanylate cyclase **stimulates the guanylyl cyclase** which is associated with nitric oxide receptors; thus an **increased quantity of CGMP is produced** which causes vasodilation. In addition to this, they also can directly stimulate the nitric oxide receptors, thereby eliciting its action. The combination of Riociguat with Sildenafil is not recommended and has shown no clinical improvement, instead increases the mortality on long runs. This class of drug is contraindicated in pregnant women.

Lines of Therapy

Combination Therapy

The rationale behind combination therapy is to **combine the two drugs with different mechanisms of action, so that an increase in efficacy is noted**. The addition may be the initial stage of therapy where two drugs are combined together or sequentially.

In a recent article published in NEJM, the combination of **Ambrisentan and Tadalafil** is said to have better physical outcomes in terms of reduction of clinical failure and improved exercise capacity when compared to monotherapy with both the drugs individually. This combination of drugs is one of the promising agents for the treatment of pulmonary hypertension.

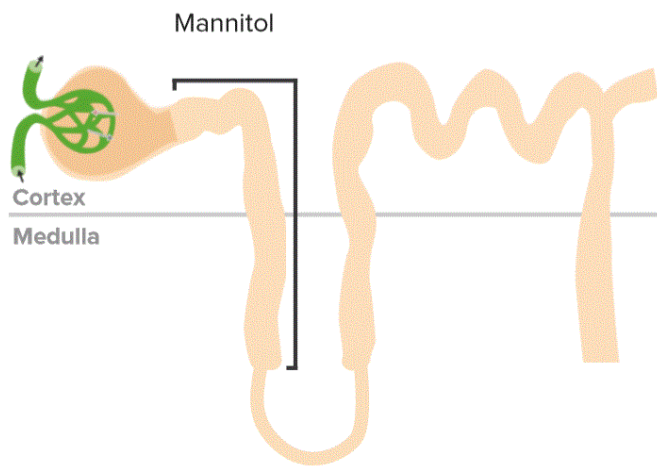
The other combination used is **Bosentan with Sildenafil**, inhaled Treprostinil with Bosentan, Epoprostenol with Bosentan, inhaled Treprostinil with Sildenafil, Epoprostenol with Sildenafil and inhaled Iloprost with Sildenafil.

Primary Therapy

The primary therapy involves the treatment of the causes of pulmonary hypertension. In the case of pulmonary arterial hypertension (PAH), in most of the cases, the main treatment is an advanced therapy. Those treatments which are relevant to pharmacological therapy will be discussed here.

Diuretics

The [diuretics](#) are given in those patients who have **fluid overload and fluid retention**. It is not routinely prescribed as it will decrease the cardiac output, which is already compromised in pulmonary hypertension.



"Mannitol" Image created by Lecturio

Mannitol:

- Acts as an osmotic agent
- Water is "pulled"
- Also works in intracranial hypertension

Acetazolamide:

- Inhibits carbonic anhydrase
- More sodium, bicarbonate, and chloride left in the tubule
- Also causes a metabolic acidosis; used in altitude sickness
- Hypokalemia
- Hyponatremia/hypochloremia

Anticoagulant

The anticoagulant, like Warfarin, is indicated in the case of **group 4 pulmonary hypertension** in which the main cause is the **formation of thrombus** in the pulmonary vasculature. There needs to be monitoring of INR in those patients who are treated with Warfarin. The Warfarin mechanism of action is by inhibiting the formation of the vitamin K dependent coagulation factors by means of inhibiting the epoxide reductase. Anticoagulants are not indicated in the case of systemic sclerosis associated with pulmonary arterial hypertension. There is a systematic review which favors the usage of the anticoagulant in the case of PAH (idiopathic).

Digoxin

Digoxin causes an increase in the contraction of the right ventricle and is warranted in **group 3 PH patients**.

Vaccination

The primary hypertension is a chronic disease so there are possibilities of getting an infection in time duration. This requires proper vaccination in accordance with the age, along with special vaccines of **pneumococcal and influenza**.

Oxygen Therapy

Oxygen therapy remains the **cornerstone of the treatment of group 3 pulmonary hypertension**, in which there is [hypoxemia](#) because of the formation of pulmonary fibrosis and change in the architecture of the lungs.

Conclusion

The treatment of pulmonary hypertension, when warranted, requires the consideration of a number of phenomena. The proper diagnosis and the pre-treatment evaluation remains the cornerstone in employing the right therapy for the treatment.

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