"Challenges in the Pharmacotherapeutic Management of Pulmonary Arterial Hypertension"

Mohammed Ismail K S[1], Jagadeesan M [2]*

[1]Mr Mohammed Ismail K S (M. Pharm- Final year student)

Department of Pharmacy Practice, SRM College of Pharmacy, SRMIST,
Kattankulathur-603 203, Chengalpattu District, Tamil Nadu
ORCID ID: 0009-0003-0726-7576
&
[2]Dr. Jagadeesan M., Pharm D., (Assistant Professor)

Department of Pharmacy Practice, SRM College of Pharmacy,
Faculty of Medical & Health Sciences SRM Institute of Science and Technology,
SRM Nagar, Kattankulathur, 603203, Chengalpattu (DT), TN, India.
ORCID ID: 0000-0003-1115-9255
Correspondence**: Dr. Jagadeesan M., Pharm D**

DOI: 10.54882/13202313202317781

Abstract

New medications are now available for patients with pulmonary arterial hypertension (PAH) that can help them improve their exercise capacity, enhance their quality of life, and delay the progression of their condition. However, these medications require careful individualized dose titration to ensure they are effective while minimizing side effects. Different routes of administration, such as intravenous (IV), subcutaneous (SC), and inhaled administration, can also present challenges for patients and healthcare providers. These challenges include the possibility of catheter-related infections (IV), infusion site pain (SC), and difficulties in adhering to frequent dosing schedules (inhaled). Temporary discontinuations may require re-titration and can even be life-threatening. In this article, we provide our recommended dose titration schemes for PAH medications that require individualized dosing for adult patients. These include medications that act on the endothelin-1 pathway (bosentan and ambrisentan), the prostacyclin pathway (epoprostenol, treprostinil, and selexipag), and the nitric oxide pathway (tadalafil and the soluble guanylate cyclase stimulator riociguat).

Keywords: pulmonary arterial hypertension , pulmonary arterial hypertension management , challenges in pulmonary arterial hypertension, dosage titration.

Introduction:

Pulmonary arterial hypertension (PAH) is a condition that causes the blood pressure in the lungs to be higher than usual, specifically over 25 mmHg[1]. If left untreated, PAH can lead to progressive increases in pulmonary vascular resistance (PVR), right heart failure, and death. PAH is more commonly diagnosed in women, typically around 50 years old, [2]. When it comes to treating PAH, it's important to get the dosage right for the medication to work effectively. However, increasing the dose can also lead to side effects, which can cause some patients to stop the treatment altogether[3]. Furthermore, the perfect dose range

varies significantly from person to person. Some PAH medications require intravenous administration, which can be inconvenient and can negatively impact the quality of life for both healthcare providers and patients. Individualized dose adjustments are crucial in hospitals and at home. In some cases, it's necessary to use approaches such as dose methods, regular monitoring, and open communication to patients to maximize the effectiveness of treatment while ensuring compliance. It's also crucial to minimize treatment side effects. In this article, we discuss the key issues and advice for customizing PAH drug doses in adult patients[4].

Currently Approved Treatment Pathways:

PAH can develop in several complex ways. The ailment initiates and progresses through various mechanisms that result in increased proliferation of smooth muscle cells, impaired function of endothelial cells, inflammatory response, and further alterations to the pulmonary vasculature. All these physiological changes lead to pathological manifestations marked by excessive narrowing of blood vessels, thickening of vessel walls due to hypertrophy, formation of scar tissues within vessel linings, and the growth of plexiform lesions[5,6].Presently, treatments for PAH target significant pathways that contribute to disease evolution, including nitric oxide, endothelin 1, and prostacyclin. In a proportion of PAH patients, excessive narrowing plays a significant part in raising resistance in the lungs' blood vessels, primarily influenced by the inflow of calcium via enduring calcium channels in the smooth muscle cells lining those vessels [7]. The standard treatment protocol for PAH involves approaching one or more of these pathways. Available options come in oral form, or via parenteral or inhalation routes. Clinical trials have objectively demonstrated that employing these therapeutic measures significantly improves the quality of life, and some even curtail mortality rates among hereditary PAH-afflicted individuals[8].

Initial treatment:

In the medical community, it is widely accepted that individuals who have been diagnosed with Pulmonary Arterial Hypertension (PAH) and do not respond to pulmonary vasodilators should undergo targeted therapy for PAH. The treatment depends on the severity of symptoms or the likelihood of clinical decline. Standard methods involve evaluating the intensity of the disease and starting oral treatment for moderate PAH. Patients with severe PAH may require uninterrupted intravenous infusion of prostacyclin [9].

WHO functional class I

As there are currently no clinical trials investigating PAH treatment for this specific patient group, it is recommended that these patients are closely monitored up to functional class II. It's important to note that this is not a call for early treatment of PAH, but rather an acknowledgement that recommending treatment for patient groups that have not been formally studied is not feasible.

WHO Functional Class II

CHEST guidelines recommend a combination of ERA and PDE5i (Ambrisentan and Tadalafil) for WHO functional class II. If the combination therapy is not possible, patients can receive ERA, PDE5i, or PDE5i as a monotherapy. Sildenafil enhances MGT, while Riociguat improves 6MWD, functional class, and delays clinical deterioration. Inhaled or parenteral prostanoids are not recommended as initial treatment for WHO functional class II.

WHO Functional Class III

The first-line therapy for WHO functional class III PAH patients is a combination of Ambrisentan and Tadalafil, which improves ERA and PDE5i, especially when 6MWD is present. Patients who can't take combination therapy can opt for Bosentan or Ambrisentan alone. Macitentan with PDE5i (sildenafil) or Riociguat may also help enhance functional class and delay clinical degradation time. For patients with higher risk, parenteral prostanoids like intravenous Epoprostenol or Treprostinil are initiated. All of these treatments have shown improvements.

WHO Functional Class IV

Ambrisentan can improve the six-minute walk distance (6MWD), enhance functional class, and delay time to clinical worsening. It should be treated solely with macitentan and PDE5 inhibitors, which are derived from sildenafil. Tadalafil can lead to improvements in 6MWT and functional class, resulting in delays in clinical degradation. Riociguat (GCS) can contribute to improving 6MWD, enhancing functional class, and delaying clinical degradation time. Intravenous epoprostenol, intravenous treprostinil, or subcutaneous treprostinil are parenteral prostanoids that are initiated in functional class III patients demonstrating signs of rapid progression or other symptoms associated with higher risk and have shown improvements. However, epoprostenol lacks proven efficacy[10].

Monotherapy:

Low to intermediate risk PAH patients usually receive oral monotherapy. Drugs are scored based on class recommendations, which have three levels of evidence: multiple large randomized clinical trials, single randomized clinical trials or large non-randomized trials, and expert opinions.To illustrate how these levels range from each other, let's consider an example of treatment for low and intermediate-risk patients. The scoring goes like I-- recommended, IIa-- should be considered, IIb-- may be considered, and III-- not recommended. These patients can be given drugs such as endothelin receptor antagonists (ERA) like Ambrisentan (I, A), Bosentan (I, A), Macitentan (I, B); Phosphodiesterase type-5 inhibitors (PDE5i) like Sildenafil (I, A), Tadalafil (I, B), Vardenafil (IIb, B), Guanylate cyclase stimulator Riociguat (I, B); or Prostacyclin receptor agonist Selexipag (I, B).On the other hand, for patients with WHO functional class III PAH belonging to low or intermediate-risk categories, oral or parenteral prostacyclin analogues like Epoprostenol are given intravenously (I, A), while Iloprost is administered via inhalation (I, B). Intravenous Iloprost (IIa, C), subcutaneous/inhaled Treprostinil (I, B), or intravenous Treprostinil (IIa, C) can also be considered.High-risk PAH patients should receive intravenous prostacyclin combined with PDE5i or ERA. Intravenous Epoprostenol is the preferred prostacyclin therapy for functional class IV PAH. Other analogues like inhaled or intravenous Iloprost can also be used. While subcutaneous/inhaled, intravenous, and oral administration to Treprostinil can be considered, the recommended levels are lower. ERA, PDE5is, or GCS should not be given orally except when patients cannot take prostacyclin infusion therapy.

Combination Therapy:

Low or intermediate risk PAH patients receive oral monotherapy based on drug class recommendations, which are graded by evidence level: multiple large, randomized trials/meta-analyses, single randomized/large non-randomized trials, and expert opinions with small/retrospective studies.To illustrate how these levels range from each other, let's consider an example of treatment for low and intermediate-risk patients. These patients can be given drugs such as endothelin receptor antagonists (ERA) like Ambrisentan (I, A), Bosentan (I, A), Macitentan (I, B); Phosphodiesterase type-5 inhibitors (PDE5i) like Sildenafil (I, A), Tadalafil (I, B), Vardenafil (IIb, B), Guanylate cyclase stimulator Riociguat (I, B); or Prostacyclin receptor agonist Selexipag (I, B).On the other hand, for patients with WHO functional class III PAH belonging to low or intermediate-risk categories, oral or parenteral prostacyclin

analogues like Epoprostenol are given intravenously (I, A), while Iloprost is administered via inhalation (I, B). Intravenous Iloprost (IIa, C), subcutaneous/inhaled Treprostinil (I, B), or intravenous Treprostinil (IIa, C) can also be considered.According to the ESC/ERS guidelines, high-risk patients should receive intravenous prostacyclin combined with PDE5i or ERA. For functional class IV PAH, intravenous Epoprostenol is the preferred prostacyclin therapy (I, A), although other analogues like inhaled or intravenous Iloprost are also used. While subcutaneous/inhaled, intravenous, and oral administration to Treprostinil can be considered, the recommended levels are lower (IIb, C). ERA, PDE5is, or GCS should not be given orally except when patients cannot take prostacyclin infusion therapy (IIb, C)[11].

Dosing titration:

Patients with PAH are prescribed drugs targeting three physiological pathways: the endothelin, prostacyclin, and nitric oxide pathways.

Agents acting on the endothelin pathway:

Endothelin-1 (ET-1) is a potent vasoconstrictor that contributes to the progression of PAH. Drugs categorized as endothelin receptor antagonists (ERAs), including Bosentan, Ambrisentan, and macitentan, counteract the vasoconstrictive effects of ET-1 by inhibiting one or both of its receptors found on vascular smooth muscle and endothelial cells.The most common side effects of these drugs are headaches and nasal congestion, which occur in 14 to 34 percent and 6 to 20 percent of patients[11,12]. Bosentan users may experience elevated liver enzymes in approximately 11% of cases, requiring close monitoring. Ambrisentan users are frequently affected by peripheral edema, while macitentan users may experience anemia in 13% of cases. This number is reduced to 7% for Ambrisentan users [13].Pregnant women should avoid using ERAs due to the potential for causing embryo-fetal toxicity. Women capable of childbearing should undergo monthly pregnancy tests and use effective contraception measures. ERAs are only available to female patients and are part of a risk assessment strategy. It is crucial to remember that ERAs can harm developing embryos and fetuses[14]**.**

Bosentan

As per the prescribing guidelines, the standard treatment of Bosentan begins with a dose of 62.5 mg, to be taken twice a day for four weeks. After that, the dose is increased to 125 mg, taken twice a day. The guidelines suggest that for patients under forty years of age and with a body mass thrice, the recommended upper limit dosage should be reduced or stopped altogether, based on the prescribing information. It has been observed that exceeding the recommended doses does not provide adequate clinical benefits to offset the higher risks of potential liver damage[14)].To reduce the risks associated with elevated transaminase levels, we initially prescribed a lower dose for the first month, after which the patient increased it to 125 mg, twice daily. However, a study of 149 subjects found comparable outcomes in terms of liver safety profiles between those who followed standard escalation protocols and those who used rapid escalation protocols [13]. Nonetheless, specialists recommend a lower dose during the initial four weeks of treatment due to the need for more conclusive research studies[15].

Ambrisentan

As stated in the dosage instructions, patients should start with Ambrisentan 5 mg once a day and gradually increase it to 10 mg once a day after four weeks of tolerating the medication. This approach applies to both administration and in combination with tadalafil or other PAH medicines. However, it is important to note that a higher prevalence of nasal blockage has been observed in patients taking the 10 mg dose.

Additionally, peripheral swelling associated with Ambrisentan appears to occur more frequently in patients over 65 years old compared to those under 65 years[13].

Macitentan

It's important to note that Macitentan doesn't require titration, and its use is limited to a single dose of 10 mg. Before starting treatment, it's recommended that liver enzymes are checked, and if necessary, re-examined later. However, there is no mandatory requirement for monthly monitoring of liver enzymes[12].

Prostacyclin Pathway Acting Agents Prostacyclin:

Prostacyclin is a substance that is naturally produced by the cells that line the blood vessels. It stimulates the PGI2 receptors in the lungs, which leads to the expansion of vascular smooth muscle, relaxation through a cyclic AMP mechanism, and ultimately results in vasodilation, anti-proliferative impacts, and anti-platelet impacts[16].However, people with Pulmonary Arterial Hypertension (PAH) have lower levels of prostacyclin in their blood vessels [5].This is why prostacyclin and similar substances are essential in treating people with PAH [17]. Since prostacyclin affects various biological processes throughout the body, it has different side effects for different patients. The most commonly experienced side effects are headaches, jaw pain, nausea, vomiting, diarrhea, limb pain, flushing, and low platelet counts [18].Administering prostacyclin intravenously is a cornerstone approach to treating advanced cases of PAH, but it has significant side effects and complications. Therefore, it should only be prescribed by healthcare professionals who specialize in PAH, and dosing requirements vary between individuals. It is essential to find an optimal balance between effectiveness and safety [14].Prostacyclin can be administered through various methods, including oral, respiratory, subcutaneous, and intravenous methods. However, parenteral dosing presents potential hardships, such as catheter-associated infections and implantation site pain, which affect long-term well-being and quality of life, thus potentially impacting adherence. Regular contact with patients receiving IV prostacyclin therapy is crucial[19].

Epoprostenol

Flolan and generic prostacyclin sodium (Veletri) are powdered forms that require reconstitution before administration through a central venous catheter using a portable infusion pump. A continuous infusion is required because their half-lives are short, lasting only 3-6 minutes. Any interruptions during this time could be life-threatening. Epoprostenol is the name of this drug, and it is known for its quick action. The initial dose is usually 2 ng/kg/min, and we will increase the dosage by 1-2 ng/kg/min every 15 minutes or less until the side effects become too much to handle or until we cannot justify the increase in dosage anymore[20]. This new approach is a lot better than what we used to do. With years of experience, we have listened to our patients and adjusted accordingly. Now, starting at 1-2 ng/kg/min, we will increase the dosage by 1-2 ng/kg/min each day until the side effects become intolerable. The initial dosage for patients coming in for release is usually between 6 and 8 ng/kg/min. Then, a slow increase must be made to get to the targeted dosage of 20-25 ng/kg/min. For most people, this can mean an extra 1-2 ng/kg/min weekly. While it is not a hard limit, if you need to give more than 8 hours of medication through a catheter, then it is best to adjust the amount given.this should be done immediately.During their stay at one of our PAH centers, patients will receive information on side effects, efficiency, and adherence to the medication. There will also be follow-ups with nurses and close surveillance in clinics. If any decline in health occurs after getting used to the current dose of epoprostenol, adjustments can be made by increasing the dosage or adding other treatments based on clinical judgment[21].High doses of prostacyclin may cause excessive side effects and high output failure. Even low doses of epoprostenol used with other therapies can lead to similar issues. While generally safe, immediate measures must be taken if too much is taken. Classically, start with half of the existing preservation dosage and increase by 1-2 ng/kg/min every 1-6 hours based on any side effects until the previous maintenance dose has been reached(22].

Intravenous Treprostinil

Treprostinil is a medication that offers a more consistent substance structure and has a half-life of 2-4 hours when given in vivo[23].It provides an alternative to IV epoprostenol, with the advantage of having a longer half-life. This allows for lower infusion rates and smaller pumps in some patients. Additionally, dressing changes can be done every 2 hours instead of every day. The recommended starting dose is 1.25 ng/kg/min (0.625 ng/kg/min if the next dose is not tolerated), with weekly increases of 1.25 ng/kg/min during the first month, according to prescribing information[19].IV Treprostinil can be titrated at a rate of 2.5 ng/kg/min each week after its introduction in the clinic. The usual starting dose for IV Treprostinil is 2 ng/kg/min, with daily increases of 2 ng/kg/min. However, in our experience at home, doses are usually increased by 2 ng/kg/min every 3-7 days until reaching a target dose of 40 ng/kg/min. Like epoprostenol, the titration period lasts around 2-3 months[24]. Depending on clinical judgment, prostacyclins may be used or combined with other treatments. Although there is no peak dose of Treprostinil, hemodynamics should be carefully monitored by dose escalation to ensure that heart output is not excessively prolonged. Like epoprostenol, Treprostinil should be reinfused if the catheter is ineffective to such an extent that drugs are not continuously administered for more than 8 hours, as outlined previously[9].

Subcutaneous Treprostinil Subcutaneous

Subcutaneous administration of Treprostinil avoids the need for an invasive central venous catheter and the titration of its recommended dose is similar to that of intravenous Treprostinil but doesn't require hospitalization. The initial dose level, although not completely established in supporting data, is equivalent to intravenous Treprostinil. Our intervention and reproducible data suggest that a rapid titration scheme can be implemented. Patients can start with a dose of 2 ng/kg/min, with 2 ng/kg/min increments given two or three times a week. This approach allows for a quick assessment of the treatment response [25]. One notable disadvantage of subcutaneous Treprostinil delivery is insertion site misuse, which is reported in 85% of patients, causing clinical anxiety. In 32% of cases, this misuse of essential sedatives resulted in treatment discontinuation in 7% of patients. It was initially used as an indicator to address insertion site misuse, but the measurement reliability relies on inconsistency. Some recent reviews suggested that a faster dose titration combined with active insertion site pain management resulted in fewer interruptions due to infusion site pain and better clinical outcomes [26].

Oral Treprostinil

Oral Treprostinil may cause osmotic changes within the Treprostinil formulation which is kept in a tablet case. It is important to exercise caution when prescribing Treprostinil tablets to patients with diverticular disease, as the tablet may get lodged in the diverticula. According to supporting data, oral Treprostinil should be administered twice daily, with a 12-hour interval between doses, or a dose of 0.125 mg three times a day, with an interval of approximately 8 hours between doses[27]. The tablets should be taken with food, and should be swallowed whole without crushing or chewing. Dosage can be increased to 0.25 mg or 0.5 mg twice daily, or 0.125 mg three times daily, every 3-4 days. It is recommended not to exceed a dose of 4 mg taken orally multiple times a day for more than 90 days. [28].Due to the risk of mild to severe adverse effects associated with rapid titration, it is advisable that oral Treprostinil and other forms of Treprostinil be prescribed by healthcare professionals experienced in this field. Common side effects of oral Treprostinil include headaches, diarrhea, ascites, bleeding, and oral discomfort. In addition, fever and gastrointestinal problems may limit the dosage[29].

Iloprost

The drug Iloprost is a type of prostacyclin that is typically administered through inhalation using the 1-neb AAD system[30]. According to the supporting data, the recommended dosage is 6-9 tablets per day, with about 2 hours between each dose. The initial dose should be 2.5 μg, with gradual increases up to a

maintenance dose of 5.0 µg. Iloprost is available in single-dose ampoules with concentrations of 10 µg/mL and 20 µg/mL, and the goal of treatment is to decrease the amount of time spent immobilized and increase the patient's overall quality of life [30].However, there are some adverse effects associated with the use of iloprost, such as flushing, persistent cough, encephalopathy, and other side effects that are typical of prostacyclin. In our intervention, adherence to the prescribed dosage might be difficult due to the frequency of hospital visits required to monitor the patient's progress[21].

Inhaled Treprostinil

An intravenous premixed oral solution is used to deliver inhaled Treprostinil, with each breath containing 6g of the medication. According to supporting evidence, the initial stage of treatment should involve taking three breaths, four times a day, for about four hours, spaced out evenly throughout the day. In addition, it is recommended to add 9 beneficial breaths every one to two weeks throughout the therapy[31]. In order to speed up the dose titration process, we suggest taking three breaths, four times a day for three days, followed by six breaths, four times a day for the next three days, and finally nine breaths, four times a day. In some cases, experienced PH professionals may assist with administering 12 breaths, four times a day, if needed. One common issue with inhaled PAH products is that patients may forget to bring their inhalers or be physically unable to use them. It is important to note that respiratory therapists cannot nebulize inhalers containing PAH medications[32].

Selexipag

Selexipag is an oral IP receptor agonist with unique properties. The prescribed dosage typically ranges from 200 µg taken twice a day, but for patients with direct hepatic impairment, it may be taken only once a day. The dosage may be increased to 200 µg twice daily per week, and the maximum dosage of selexipag is 1600 µg taken twice daily. If patients experience any side effects that limit the dosage, the dose should be reduced to the previous accepted level. Selexipag should be added to the patient's existing medication regimen to help them tolerate the development[33]. For patients with tolerance concerns, a slower schedule may be more appropriate. The normal dosage schedule involves taking it twice a day over one-week intervals. In cases where tolerance issues arise, Selexipag should be discontinued until the additional dose measurement is taken. If a patient miss taking Selexipag for 3 or more days, they should start with a low dose and re-titrate. If Selexipag is withdraw, it should be resumed when elective treatment is offered. To ensure proper care, Power Pharmacy attendants actively monitor patients who adhere to therapy, investigate side effects, and monitor for possible contraindications like brain pain, running, oral abuse, or sickness. In some instances, patients may benefit from mild analgesics [34].

Agents acting on the nitric oxide pathway:

Nitric oxide enhances the cyclic GMP system in smooth muscle cells by binding to soluble guanylate cyclase. This has an anti-proliferative and vasodilatory effect on the airways, leading to increased relaxation. Supporting data for sildenafil recommends taking 5 mg or 20 mg three times a day, spaced 4-6 hours apart, and avoiding overdose. Similarly, data shows that tadalafil can be calibrated at 40 mg once daily but starting with 20 mg per day for the first week before increasing to 40 mg per day [35].We have struggled with finding the right dosage during treatment but found that following the titration schedule utilized in the aspiration test is effective for patients who consent to dual therapy with tadalafil and Ambrisentan[36]. We recommend starting with a single initial measurement of 5 mg of Ambrisentan and 20 mg of Tadalafil every day, with continued monitoring of Tadalafil levels[37,38].

Riociguat

According to supporting data, riociguat should be initiated at a dose of 1 mg three times daily in hypertensive patients, which can then be increased by increments of 0.5 mg three times daily every two weeks. The maximum recommended dose is 2.5 mg three times daily. If any symptoms of hypotension are observed, a dose of 0.5 mg should be used instead. Patients with a blood pressure reading above 95 mmHg and no signs of hypertension can attempt to increase the dosage. Although there is already clear evidence in support of this protocol, ongoing research is still being conducted to provide more information as time goes on[39].

Conclusion:

The accessibility of drugs designed to improve the health of patients with pulmonary arterial hypertension (PAH) has significantly improved. However, administering the correct dosage of these medications requires careful attention. Taking too much of the medication can be hazardous, while taking too little may render it ineffective. Recent research has demonstrated that gradually increasing the dosage until it reaches an optimal level is the best way to ensure that patients benefit from the medication without putting themselves at risk. When administered correctly, PAH medication can maximize its benefits and prevent withdrawal effects entirely. Nonetheless, the administration of these medications has its challenges. Patient education must be thorough to ensure that they understand how it operates and the importance of adhering to the medication schedule. There are other risks involved, such as severe life-threatening side effects and treatment interruptions that could lead to additional complications.

Conflict of Interest: None

Funding: None

References:

1. Coons JC, Pogue K, Kolodziej AR, Hirsch GA, George MP. Pulmonary Arterial Hypertension: a Pharmacotherapeutic Update. Curr Cardiol Rep. 2019 Nov 22;21(11):141.
2. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and Diagnosis of Pulmonary Hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25_Supplement):D42–50.
3. M. Kingman, C. Archer-Chicko, M. Bartlett, J. Beckmann, R. Hohsfield, S. Lombardi, Management of prostacyclin side effects in adult patients with pulmonary arterial hypertension, Pulm. Circ. 7 (3) (2017) 598–608.
4. Lombardi S, Kingman M, Duncan M, Berngard SC, Fernandes T. Titration of pulmonary arterial hypertension therapeutics: Experience-based recommendations. Respir Med. 2018 Oct;143:139–46.
5. Humbert M, Morrell NW, Archer SL, Stenmark KR, MacLean MR, Lang IM, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. J Am Coll Cardiol. 2004 Jun 16;43(12_Supplement):S13–24.
6. Sitbon O, Morrell NicholasW. Pathways in pulmonary arterial hypertension: the future is here. Eur Respir Rev. 2012 Dec;21(126):321–7.
7. Medarov BI, Judson MA. The role of calcium channel blockers for the treatment of pulmonary arterial hypertension: How much do we actually know and how could they be positioned today? Respir Med. 2015 May 1;109(5):557–64.
8. Mayeux JD, Pan IZ, Dechand J, Jacobs JA, Jones TL, McKellar SH, et al. Management of Pulmonary Arterial Hypertension. Curr Cardiovasc Risk Rep. 2020 Nov 27;15(1):2.

9. Vazquez ZGS, Klinger JR. Guidelines for the Treatment of Pulmonary Arterial Hypertension. Lung. 2020 Aug 1;198(4):581–96.
10. Klinger JR, Elliott CG, Levine DJ, Bossone E, Duvall L, Fagan K, et al. Therapy for Pulmonary Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report. CHEST. 2019 Mar 1;155(3):565–86.
11. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A et al (2016) 2015 ESC/ERS guidelines for the diagnosis and treat ment of pulmonary hypertension: the joint task force for the diag nosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Soci ety (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37(1):67–119.
12. Rubanyi GM, Polokoff MA. Endothelins: Molecular biology, biochemistry, pharmacology, physiology, and pathophysiology. Pharmacol Rev. 1994;46(3):325–415.
13. Suntharalingam J, Hodgkins D, Cafferty FH, Hughes RJ, Pepke-Zaba J. Does rapid dose titration affect the hepatic safety profile of Bosentan? Vascul Pharmacol. 2006 Jun 1;44(6):508–12.
14. Mubarak KK. A review of prostaglandin analogs in the management of patients with pulmonary arterial hypertension. Respir Med. 2010 Jan 1;104(1):9–21.
15. Galie N, McLaughlin VV, Rubin LJ, Simonneau G (2019) An overview of the 6th world symposium on pulmonary hyperten sion. Eur Respir J.
16. Kingman MS, Lombardi S. Management of the patient with pulmonary arterial hypertension receiving intravenous prostacyclin. J Infus Nurs. 2014;37(6):442–51.
17. McLaughlin VV, Palevsky HI. Parenteral and Inhaled Prostanoid Therapy in the Treatment of Pulmonary Arterial Hypertension. Clin Chest Med. 2013 Dec 1;34(4):825–40.
18. Rich S, McLaughlin VV. The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. J Am Coll Cardiol. 1999 Oct 1;34(4):1184–7.
19. Bartolome SD, Sood N, Shah TG, Styrvoky K, Torres F, Chin KM. Mortality in Patients With Pulmonary Arterial Hypertension Treated With Continuous Prostanoids. Chest. 2018 Sep 1;154(3):532–40.
20. Skoro-Sajer N. Optimal Use of Treprostinil in Pulmonary Arterial Hypertension. Drugs. 2012 Dec 1;72(18):2351–63.
21. Remodulin® [prescribing Information]. United Therapeutics Corporation, Research Triangle Park, NC; December, 2014.
22. E. Grünig, N. Benjamin, T.J. Lange, U. Krueger, H. Klose, C. Neurohr, H. Wilkens, M. Halank, H.J. Seyfarth, M. Held, A. Traube, M. Pernow, E.R. Grover, B. Egenlauf, F. Gerhardt, T. Viethen, S. Rosenkranz, Safety, tolerability and clinical effects of a rapid dose titration of subcutaneous treprostinil therapy in pulmonary arterial hypertension: a prospective multi-centre trial, Respiration 92 (6) (2016) 362–370.
23. Orenitram® [prescribing Information]. United Therapeutics Corporation, Research Triangle Park, NC; January 2017.
24. F.F. Rahaghi, J.P. Feldman, R.P. Allen, V. Tapson, D.L. Zwicke, Z. Safdar, V.P. Balasubramanian, S. Shapiro, M. Mathier, J.M. Ewing, M.M. Chakinala, R.J. White, The Delphi Process in the creation of a consensus statement for practical use of orenitram, Am. J. Respir. Crit. Care Med. 191 (2015) A4774.
25. N.S. Hill, D. Badesch, R.L. Benza, T.A. D'Eletto, H.W. Farber, M. Gomberg-Maitland, P.M. Hassoun, I. Preston, Perspectives on oral pulmonary hypertension therapies recently approved by the U.S. Food and Drug Administration, Ann. Am. Thorac. Soc. 12 (2) (2015) 269–273.
26. Ventavis® [prescribing Information]. Actelion Pharmaceuticals US, Inc., South San Francisco, CA; October 2017.

27. Tyvaso® [prescribing Information]. United Therapeutics Corporation, Research Triangle Park, NC; October 2017.
28. Waxman AB, Zamanian RT. Pulmonary Arterial Hypertension: New Insights Into the Optimal Role of Current and Emerging Prostacyclin Therapies. Am J Cardiol. 2013 Mar 4;111(5, Supplement):1A-16A.
29. M.J. Richter, H. Gall, J. Grimminger, F. Grimminger, H.A. Ghofrani, Selexipag for the treatment of pulmonary arterial hypertension, Expet Opin. Pharmacother. 17 (2016) 1825–1834.
30. N. Galiè, J.A. Barberà, A.E. Frost, H.A. Ghofrani, M.M. Hoeper, V.V. McLaughlin, A.J. Peacock, G. Simonneau, J.L. Vachiery, E. Grünig, R.J. Oudiz, A. Vonk Noordegraaf, R.J. White, C. Blair, H. Gillies, K.L. Miller, J.H. Harris, J. Langley, L.J. Rubin, AMBITION Investigators. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension, N. Engl. J. Med. 373 (9) (2015) 834–844.
31. Wharton J, Strange JW, Møller GMO, Growcott EJ, Ren X, Franklyn AP, et al. Antiproliferative effects of phosphodiesterase type 5 inhibition in human pulmonary artery cells. Am J Respir Crit Care Med. 2005;172(1):105–13.
32. Makowski CT, Rissmiller RW, Bullington WM. Riociguat: A Novel New Drug for Treatment of Pulmonary Hypertension. Pharmacother J Hum Pharmacol Drug Ther. 2015;35(5):502–19.