DOI: 10.1002/pul2.12012

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Differences in health policies for drug availability in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension across Latin America

Mauricio Orozco-Levi[1,2,3,4] | **Jorge Cáneva**[5] | **Caio Fernandes**[6] | **Ricardo Restrepo-Jaramillo**[7] | **Nayeli Zayas**[8] | **Rafael Conde**[4,9] | **Mirta Diez**[10] | **Carlos Jardim**[6] | **Manuel C. Pacheco Gallego**[4,11,12,13,14] | **Luciano Melatini**[15] | **Héctor Valdéz**[16] | **Tomás Pulido**[8]

[1]Respiratory Department, Hospital Internacional de Colombia, Bucaramanga, Colombia

[2]EMICON Research Group, MINCIENCIAS, Bogotá, Colombia

[3]Universidad de Santander (UDES), Bucaramanga, Colombia

[4]Red Colombiana de Hipertensión Pulmonar (HAPred.co), Colombia

[5]Respiratory Department, Hospital Universitario Fundación Favaloro, Buenos Aires, Argentina

[6]Pulmonary Division, Pulmonary Circulation Unit, Pulmonary Division, Heart Institute, University of São Paulo Medical School, São Paulo, Brazil

[7]University of South Florida, Tampa, Florida, USA

[8]Cardiopulmonary Department, National Heart Institute, Mexico City, Mexico

[9]Critical Medicine and Intensive Care, Pulmonology, Vascular Pulmonary Center, Fundación Neumológica Colombiana, Bogotá, Colombia

[10]Cardiology Department, Instituto Cardiovascular Buenos Aires, Buenos Aires, Argentina

[11]Colombian Association of Pulmonology and Chest Surgery, Pereira, Colombia

[12]Universidad Tecnológica de Pereira, Pereira, Colombia

[13]Universidad Autónoma de las Americas, Pereira, Colombia

[14]Respiremos, Respiratory Care Unit, Pereira, Colombia

[15]Respiratory Medicine, Center for Advanced Complexity Respiratory Studies, Bahia Blanca, Argentina

[16]Pulmonary Function Department, Mexican Social Security Institute, Monterrey City, Mexico

Correspondence
Mauricio Orozco-Levi, Respiratory Department, Hospital Internacional de Colombia, Bucaramanga 68 00 05, Colombia.
Email: mauricio.orozco.levi@gmail.com

Funding information
Bayer South America, Bogota, Colombia

Abstract

Treatment for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension in Latin America differs between countries, with regard to disease etiology, health insurance coverage, and drug availability. A group of experts from Latin America, met to share regional experiences and propose possible lines of collaboration. The available evidence, regional clinical practice data, and the global context of the proceedings of the 6th World Symposium on Pulmonary Hypertension, held in Nice, France, in February 2018, were analyzed. Here, we discuss some priority concepts identified that

could guide transnational interaction and research strategies in Latin America: (1) despite being evidence-based, the 6th World Symposium on Pulmonary Hypertension proceedings may not be applicable in Latin American countries; (2) proactive identification and diagnosis of patients in Latin America is needed; (3) education of physicians and standardization of appropriate treatment for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension is vital; (4) our clinical experience for the treatment strategy for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension is based on drug availability in Argentina, Brazil, Colombia and México; (5) there are difficulties inherent to the consultation of patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, and access to treatment; (6) the importance of data generation and research of Latin American-specific issues related to pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension is highlighted.

KEYWORDS
drug combinations, hypertension, pulmonary, risk assessment

INTRODUCTION

Pulmonary hypertension (PH) is a rare, progressive disease that imposes a challenge for patients with a high mortality rate, and significant costs of care.[1–6] In recent decades, great advances have been made in the diagnosis and treatment of PH, mainly in subpopulations with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).

Treatment of PH has evolved substantially in the past few years, with new emergent treatment strategies supported by the knowledge of the disease and newly available agents. Treatment algorithms have been stated by the American College of Chest Physicians, the European Society of Cardiology, the European Respiratory Society, and a panel of experts in the *6th World Symposium on Pulmonary Hypertension (WSPH)*,[1,7–10] which are individualized by many factors (severity of disease, route administration, comorbidities, clinical preferences, and treatment goals, among others)[11] with long- and short-term follow-up that supports its improvement in symptoms, prognosis, and quality of life. Nevertheless, some subpopulations like Latin-American are not included in the treatment algorithms, since they have regional characteristics, inequitable access to health care, and therapies that are specific to the region.[12]

In April 2019, a group of experts in the treatment of PH in Latin America met to share their individual experiences and to discuss possible topics for collaboration. The experts analyzed the available evidence and regional clinical practice data, all within the context of the recent *WSPH*, which took place in Nice, France, in 2018.[13] This group of Latin America experts, discussed main concepts related to the differences in healthcare policies, drug availability in PAH and CTEPH in Argentina, Brazil, Colombia, and México, including treatment strategies involved in multiple therapeutic pathways (intra and inter), which are relevant for patients with progressive disease. Drug "transition" was considered as any change from a specific PH medication for other drugs acting on a different therapeutic pathway, whereas drug "switching" was considered as any change from a specific PH medication for other drugs acting on the same pathway. This meeting resulted in a series of expert recommendations covering the diagnosis, treatment, and monitoring of PH; and the objective of the present article is to present these expert recommendations.

HEALTH POLICIES ACROSS LATIN AMERICA COUNTRIES

Argentina

National health system and PH

Argentina has a comprehensive network of specific care for patients with PH, but access to provisions for diagnosis and specific treatments varies from one payer to another. The National Constitution ensures universal

free-of-charge health coverage to all citizens, regarding consultations and treatment in public hospitals. But a percentage of the population also has coverage through private healthcare insurance and/or labor unions; the latter includes medical coverage for workers with a specific occupation. These two types of coverage overlap within public health care making the healthcare coverage complex. For those patients who have private healthcare insurance or labor union coverage, the Compulsory Medical Plan (or PMO)/Resolution 1996, offers a basic pool of benefits assured by the Ministry of Health and is available for these patients. In other cases, funds to finance the costs of PAH-specific medication can be obtained through a judicial right-to-health process ("constitutional remedies").

Nowadays, PH has been considered a rare disease due to its low prevalence (≤1:2000) and by Law 26.689, patients receive free of charge access to specific medications. This represents an advance in the management of PH and led the Ministry of Health in 2019 to recognize a system to financially cover the cost of specific PAH and CTEPH treatments.[14]

Epidemiological and clinical data

Argentina has a single-center PAH registry (Fundación Favaloro)[15] and a multicenter, collaborative PH registry (Registro Colaborativo de Hipertensión Pulmonar en Argentina [RECOPILAR]) created by five scientific societies (Argentine Federation of Cardiology, Argentine Association of Respiratory Medicine, Argentine Society of Cardiology, Argentine Society of Pediatrics, and Argentine Society of Rheumatology).[16] These registries, as large international PAH registries, are the collaborative effort to provide national clinical data information. Between 2009 and 2014, the RECOPILAR registry enrolled 627 patients with any type of PH, of whom 17.5% had no state-funded (public) healthcare coverage. The most common type of PH was PAH (64%). Of these patients, 19.5% received no medication, and 80.5% were treated with specific drugs (PDE5is, 71%; endothelin receptor antagonists [ERAs], 54%; and prostanoids, 14.3%); with 50.9% receiving combination therapy and 29.6% receiving monotherapy. The three-year survival in patients with PAH was 82.8%.

Regarding CTEPH, there is widespread availability of tools for diagnosing and treating this population with off-label PAH-targeted drugs but limited medical centers where pulmonary endarterectomy (PEA) and balloon pulmonary angioplasty (BPA) can be performed. A new update of the RECOPILAR registry showed that 36.1% of patients with CTEPH received no therapy and the remaining received off-label PAH-targeted drugs (PDE5is, 55.7%; ERAs, 27.9%; prostanoids, 9.8%), with 24.6% receiving combination therapy and 39.3% receiving monotherapy (unpublished data).

Although the registry did not collect data on the switch between drugs in patients with PAH and CTEPH (i.e PDE5i, sGC stimulator, ERAs, Prostanoids), this strategy is common, and transition from one class to another occurs regularly depending on the goal-oriented algorithms matched with the risk stratification scores, making the transition between drug classes in CTEPH and PAH feasible.[16]

Drug availability

All internationally licensed PAH-specific treatments, except oral beraprost and oral treprostinil, are available in Argentina, in either their original or generic formulations (Table 1).[14] The main barriers to treatment are cost and bureaucracy, due to the complexity of the approval process by healthcare providers, as mentioned above.

Brazil

National health system and PH

The Brazilian healthcare system has two primary sources of funding: the public and the private; through health maintenance organizations. Under Brazilian law, however, the private healthcare system has no obligation to pay for CTEPH and PAH therapy, especially oral drugs in the outpatient setting. Therefore, regardless of their personal resources, most patients with PAH receive treatment funded by the public health system.

Patients' access to PAH-specific therapies is regulated by a national protocol, produced and published by the Ministry of Health, which was updated in 2014.[17] The protocol prioritizes monotherapy and has been heavily criticized by the PAH reference centers in Brazil for its lack of scientific rigor. The protocol also recommends a hierarchical pathway for PAH treatment, with sildenafil or iloprost recommended as first-line therapy. However, iloprost was not commercially available in Brazil in 2014, and, as a result, drugs affecting the prostacyclin pathway have rarely been used in Brazil. If a patient does not improve with sildenafil, the protocol recommends switching to an ERA (ambrisentan or bosentan), a recommendation not adequately studied in any PAH trial and not endorsed by any national or international guideline for PAH.[1,18] Moreover, the Brazilian protocol

TABLE 1 PAH-specific therapies available in Latin America[a]

Drug			Argentina	Brazil	Colombia	Mexico
ET1 antagonist	Bosentan		62.5 and 125 mg	62.5 and 125 mg	62.5 and 125 mg	62.5 and 125 mg
	Ambrisentan		5 and 10 mg	5 and 10 mg	5 and 10 mg	5 and 10 mg
	Macitentan		10 mg	10 mg	10 mg	10 mg
PDE5 inhibitors	Sildenafil		Generic products	Generic products	Generic products	Generic products
			Revatio®[b] is not available	Revatio® is not available	Revatio® is not available	Revatio® is available
	Tadalafil		20 mg	20 mg	20 mg	20 mg
sGC stimulators	Riociguat		0.5, 1, 1.5, 2, and 2.5 mg	0.5, 1, 1.5, 2, and 2.5 mg	1.0–2.5 mg	0.5, 1, 1.5, 2, and 2.5 mg
IP receptor agonists	Selexipag		200, 400, 600, 800, and 1600 μg	✗	✗	200, 400, 800,1000, 1200, and 1600 μg
Prostacyclin analogs	Epoprostenol		✓	✗	✓	✗
	Treprostinil	IV/SC	✓	✗	✓	✓
		Oral	✗	✗	✗	
		INH	✓	✗	✗	✗
	Iloprost	INH	✓	✓	✓	✓
Coverage						
Type			Insurance company, labor unions and central government	Partial local government	Total central government	Partial government: ISSSTE, SEDENA, SEMAR, PEMEX, IMSS, SSA, Insurance
Registry						
Name[b]			RECOPILAR		HAPred.co	REMEHIP

Abbreviations: ERA, endothelial receptor antagonist; ET1, endothelin-1; HAPred.co, Colombian Network of Pulmonary Arterial Hypertension; IMSS, Mexican Social Security Institute; INH, inhalation; IP, prostaglandin I2; ISSSTE, Institute of Social Security and Services of State Workers; IV, intravenous; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase-5 inhibitor; PEMEX, Medical Services of Mexican Petroleum; RECOPILAR, first collaborative registry of pulmonary hypertension in Argentina; REMEHIP, Mexican Pulmonary Hypertension Registry; REVEAL, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management; SC, subcutaneous; sGC, soluble guanylate cyclase; SSA, Secretary of Health and Assistance; SEDENA, Secretary of National Defense; SEMAR, Naval Secretary.

[a]There are no data available for other Latin American countries in this document.

[b]Revatio® (Sildenafil) is manufactured by Pfizer.

does not allow for any form of upfront or sequential combination therapy. Treatment of non-PAH types of PH is also not reimbursed, and no medical therapy for CTEPH is indicated in the protocol. The protocol is currently being updated, and a new version is expected in late 2021. Because of this, some states particularly São Paulo and Bahia, have implemented local protocols for PAH therapy, allowing combination therapy with an ERA and sildenafil, and there is some discussion regarding permitting new prostacyclin pathway-targeted agents for patients with PAH who do not reach prespecified therapeutic goals. This recommendation follows the most recent international guidelines for PAH therapy,[1] but patients in Brazil are still denied access to intravenous prostanoids, a crucial element of drug therapy for patients with severe PAH.[1,18]

Several geographic and historical characteristics affect PAH treatment in Brazil. It is the fifth-largest country in the world, corresponding to 43.7% of the population in South America,[19] and its population is not evenly distributed throughout the country. Health assistance usually follows population distribution, and in Brazil, this is no different. Therefore, several thousand square kilometers of Brazil (mainly in the west of the country), are not adequately covered by healthcare providers. PAH reference centers follow the same pattern of distribution as health providers and are mostly located in eastern Brazil along the

coast, in the south and southwest.[20,21] As PAH centers are not equally distributed throughout the country and PAH patients are evaluated here; some patients must travel thousands of kilometers to be evaluated and treated adequately. Furthermore, there is no formal definition of a PAH reference center in Brazil, so the number of patients and the expertise of the attending physicians differs from center to center. Indeed, many Brazilian interventional cardiologists are not familiar with right ventricular and pulmonary artery hemodynamics, which are, therefore, not measured routinely; and parameters such as abnormal and often implausible pulmonary artery wedge pressures are unseen, delaying diagnosis and initiation of PAH-specific therapy, and negatively impacting patient outcomes.

Regarding CTEPH, there are several hurdles, such as the unbalanced availability of ventilation/perfusion scintigraphy and an insufficient number of centers where PEA and/or BPA can be performed. Of note, São Paulo, the largest city in terms of population, has the oldest and largest program of PEA in Latin America, at the Instituto do Coração in the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, which started in the 1990s and performs around 40 PEAs per year. However, in other large cities, PEA and BPA are rather rare due to a lack of resources.

Epidemiological and clinical data

There is no national database to provide reliable information about the epidemiology of PAH and CTEPH in Brazil. Despite the absence of reliable epidemiologic data, patients with CTEPH and PAH in Brazil face two obstacles: general practitioners who are unfamiliar with the disease, leading to delayed diagnosis; and difficulty accessing to right heart catheterization (RHC), a crucial tool for PAH and CTEPH diagnosis and guiding treatment decisions.

Some centers in Brazil took part in the REPLACE study,[22] which investigated the effect of switching from PDE5is to riociguat in patients with PAH with unmeet treatment goals. Early results from REPLACE showed that more patients who switched to riociguat achieved the composite primary endpoint of clinical improvement in the absence of clinical worsening, compared with patients continuing on PDE5is (41% vs. 20%, respectively).[23] Unfortunately, there is no consistent experience to report on switching from PDE5i to riociguat as it is not available in the public health system, where most patients are treated.

Drug availability

As stated before, PAH-specific therapies are regulated by a national protocol, produced and published by the Ministry of Health, and paid by the public health care system. The only reimbursed PAH-specific drugs in Brazil are sildenafil, ambrisentan, or bosentan (Table 1). Other PAH-specific drugs, such as selexipag, are approved for use in Brazil but are not reimbursed by either national or local government. Riociguat is not licensed for PAH treatment in Brazil. For patients with CTEPH, riociguat and macitentan are approved for use in Brazil, but neither is reimbursed by any government entity.

In conclusion, patients with PAH in Brazil face several barriers to treatment. These include the unfamiliarity of general practitioners with the disease, difficulties in diagnosis and poor access to RHC, few PAH reference centers with variable expertise, long distances to reach attention, and few available PAH-specific drugs, of which even fewer are reimbursed by the government. These difficulties, superimposed on the severity and natural course of PAH, may aggravate an already complex condition.

Colombia

National health system and PH

From an economic point of view, the Colombian healthcare system theoretically guarantees that all drug prices are limited by regulation from an official government entity, and also that treatment is available as part of the health benefits plan (*plan de beneficios en salud*).[24] This regulation provides the advantage of universal access under the national health economic coverage plan, regardless of the individual patient insurance plan. It has, therefore, been possible to acquire important clinical experience and data on treatment escalation, combination, and drug transitioning; regarding both patient outcomes and administrative aspects of the labeled indications, prescriptions issued and dispensed, and continuity of treatment.

There are at least six expert centers in Colombia that provide complete diagnostic workup for CTEPH and PAH and operability assessment for CTEPH. These centers also perform PEA and experience with BPA is developing.

Epidemiological and clinical data

Although there are no consolidated multicenter data on drug transitions in PAH in Colombia, preliminary data have been compiled through a multidisciplinary and

multi-institutional network. As of April 2020, unpublished data based on 20 centers with more than 550 patients reported that intrapathway transitions between ERAs have occurred in 23% of patients, switches between prostanoids in 30% of patients, and switching from a PDE5i to riociguat in 61% of patients (personal communication from HAPred.co, Red Colombiana de Hipertensión Pulmonar). The main reasons for these changes were clinical (poor outcomes, disease progression, or failure with previous treatment) or administrative (availability of previously prescribed drugs). Some of our experience regarding switching to riociguat has been published in the CAPTURE study,[25] an international, multicenter, uncontrolled, retrospective chart review that collected data from patients with PAH who were inoperable or had persistent/recurrent CTEPH; and switched to riociguat from another PH-targeted medical therapy.[25] In this study, the majority of patients switch from a PDE5i to riociguat, with lack of efficacy as the most common reason. Physicians used the recommended 24-h wash-out period when switching patients from sildenafil to riociguat, but a slightly longer period than the recommended 48-h wash-out period for tadalafil. The majority of patients did not have dose adjusted as recommended. The study showed that switching from another PH-targeted therapy to riociguat may be feasible in clinical practice in the context of the current recommendations.[25] No data on the safety or efficacy of other transitions in Colombia are available.

Drug availability

Colombia is one of the Latin American countries with the highest availability of drugs approved for the treatment of PAH and/or CTEPH (Table 1); only the prostanoid beraprost is not available. The prostacyclin receptor antagonist selexipag was approved in April 2021.

Given the number of PAH treatments available in Colombia and the possible combination regimens, several intrapathway and/or interpathway changes scenarios are feasible. These theoretical possibilities demonstrate a total of 65 intra intrapathway combinations that 65 could be used when prescribing mono, dual, or triple sequential therapies during the natural history of the patient's disease. There is no clear strategy generated for interpathway transition, but there is also no strategy for restricting this practice. For CTEPH, however, the transition possibilities are usually lower because for inoperable patients or patients with persistent or recurrent CTEPH.

In conclusion, Colombia has a healthcare system that guarantees the pharmacologic and surgical options required for the treatment of patients with PAH and CTEPH, so it is possible to perform intrapathway switching and interpathway transition. However, there are limitations in accessing reference centers for the appropriate diagnosis and treatment and a lack of data evaluating treatment strategies such as switching and transition.

Mexico

National health system and PH

The national healthcare system of Mexico was first established in 1943 and is now composed of six national public bodies: the Mexican Social Security Institute (IMSS), which covers >80% of the population; the Institute of Social Security and Services of State Workers (ISSSTE, with 18% of the population); the Social Security Institute for the Armed Forces (SEDENA, SEMAR; the Medical Services of Mexican Petroleum (PEMEX; with 1% of the population); the Secretary of Health and Assistance (SSA); and the National System for the Integral Development of the Family (DIF; with 2% of the population). Also, a minority of the population has private insurance, which not always covers specific drugs for PAH. Access to healthcare resources for diagnosis and treatment depends on the public healthcare system to which they belong. Nevertheless, there are approximately 30 million people not covered by any of these systems.[26,27]

The current national guidelines for PAH, need amending to include all PAH-specific drugs that are available in Mexico and to improve the diagnosis and referral of patients so they can be fast-tracked to expert centers. One of the greatest challenges facing the current Mexican healthcare system is to find alternatives that allow the integration of a service that is currently disintegrated, and which results in an increased cost to the system. The unification of this system would provide all patients with the same treatment opportunities thus allowing universality and equity of health rights.

Epidemiological and clinical data

The Mexican Pulmonary Hypertension Registry (REMEHIP), includes 23 centers, and it is the first prospective national registry to include incident (51.5% of cases) and prevalent (48.5%) cases of CTEPH and PAH.[28] Of 796 patients, 684 (85.9%) were diagnosed as Group 1 (PAH) and 112 (14.1%) as Group 4 (CTEPH), with the most frequent PAH etiologies being idiopathic

PAH ($n = 248$), PAH associated with congenital heart disease ($n = 112$), and PAH associated with connective tissue disease ($n = 112$). The median age was 41 years and 66.6% of patients were in World Health Organization functional class (WHO FC) I and II. REMEHIP provides a link between the needs of patients with CTEPH and PAH and the Mexican healthcare system.

Data from this study also showed that most patients (85.1%) at enrollment were receiving PAH-specific therapy, being the most common treatment PDE5i (67.7%), followed by ERAs (33.0%), prostanoids (9.1%), and sGC stimulators (3.4%). Monotherapy was the most frequent strategy (59.0%) followed by dual combination therapy (24.4%), with triple combination therapy (1.6%) being less common. In our clinical experience, 69.2% of patients with CTEPH have received off-label treatment with PAH-targeted drugs (PDE5i 49.2%, ERA 15.8%, prostanoids 4.2%) with only 7.2% of patients receiving the sGC stimulator riociguat.

The transition between PAH-specific drugs is infrequent and experience is limited. Five years ago, the Mexican government, due to administrative issues, supported switching within the ERA drug class (bosentan to macitentan) for patients with PAH. In patients who switched from bosentan to macitentan, an increase in 6-min walk distance and WHO FC was observed. Recently, riociguat was approved for PAHGroup 1, but only in one healthcare system; patients are occasionally transitioned to riociguat from other PAH-specific drugs, but outcome data are not yet available for these patients. Two Mexican centers recently participated in the REPLACE study,[22] the results of which are awaited.

For the last 31 years, the PEA program set up a unique center in Mexico (Ignacio Chávez National Heart Institute) and 99 procedures have been performed to date for patients with CTEPH. More recently, the BPA program was started 1 year ago with eight patients enrolled to date, who have received three or four procedures each.

Drug availability

In general, patients in Mexico with PAH or CTEPH receive some form of specific treatment, although with the limited availability of certain drugs (Table 1) and an undescribed risk of undertreatment.

In conclusion, patients with PAH in Mexico suffer from lack of awareness about the disease, lack of knowledge about expert centers, and insufficient diagnosis with not all assessments performed (including RHC). Referral to expert centers is limited and treatment is heterogeneous. This delay in the correct PH identification and timely treatment greatly impacts the outcome of the disease.

DISCUSSION

This document summarizes the contributions of an expert panel on critical and fundamental concepts regarding the present situation and experience of clinical practice with PAH and CTEPH, and drug transitions in several Latin American countries. The five main concepts set out below could provide strong guidance to orient research and health policies for PAH and CTEPH treatment in Latin America.

The *first important concept* of discussion raised the issue that, despite the evidence base, the WSPH proceedings may not be applicable in our countries. There are genomic and epigenomic data that, based on other diseases such as cancer, make questionable the direct application of available scientific evidence in our population. Nevertheless, in the absence of data supporting this limitation, physicians in Latin America should adopt the current guidelines.

The *second concept* is related to the proactive identification and diagnosis of patients with PH. Given the low prevalence of PH, it is indisputable that there is little benefit from active searching in routine clinical practice. For this reason, searching is restricted to groups at high risk of PH (e.g., those with conditions such as systemic sclerosis, pulmonary embolism, congenital heart disease). If, however, we wait for patients to seek medical help for dyspnea, right heart failure, or syncope, they will probably have been affected for a long time and this PAH will be diagnosed very late.

The *third concept* to highlight is that there is a need to educate physicians and disseminate advice to standardize treatment of CTEPH and PAH in the different Latin American countries, where there seems to be an overprescription of PAH-specific drugs for other forms of PH (particularly that related to left heart disease and lung diseases and/or hypoxia).

The *fourth concept* relates to the difficulties inherent in the consultation, access, and follow-up of patients with PAH and CTEPH. Due to the intrinsic complexity of their condition, these patients demand more time in consultations, which requires clinics to be organized in a way that makes this possible. Consultations cannot always be elective, but in many cases multiple consultations are required, consuming multiple diagnostic resources, all of which place an increased burden on clinics and healthcare systems, potentially to the detriment of other patients. Consequently, the consensus

proposal is for the promotion of specialized standardized consultations for patients with CTEPH and PAH.

The *fifth concept* discussed in the consensus group considered the innovative potential of Latin America-specific research. There are questions such as the potential role of altitude, exposure to biomass smoke, diet, and access to treatments, among others, that may substantially modify a patient's response to PAH and CTEPH treatments. No data on these issues are available in the published literature. A networked Latin America group could generate relevant data to solve common or specific regional problems in an innovative way.

Differences in health policies for drug availability in PAH and CTEPH among Latin American countries facilitate the use of other management strategies in patients with PH. Switching between drug pathways is done to potentially obtain better outcomes in patients whose clinical condition is not improving or even worsening despite existing treatment, for example, transition from a PDE5i to an sGC stimulator due to the critical loss of nitric oxide synthesis as part of the progression of PAH, which renders PDE5i therapy ineffective. Such a transition is recommended for patients who do not achieve treatment goals based on risk assessment tools such as the REVEAL risk score or ERS risk calculator.[29] Moreover, the recently published REPLACE study results confirm that switching to riociguat in patients who do not achieve treatment goals despite stable PDE5i therapy is associated with clinical improvement in significantly more patients than those who continue their existing PDE5i.[23] The possibility of adverse events and interactions with other drugs highlights the need for patients to have access to more than one drug acting on each pathway.

Latin American countries have different healthcare systems, which translates into different drug availability and access. The countries described here are mainly composed of two health systems: the private and the public. Then each system may subdivide according to policies in each country. Likewise, access and approval of medication may be regulated in some countries by laws, in others by protocols, or not regulated at all. Additionally, there are disparities across Latin America, with some countries having access to all 14 drugs currently available for PAH, while others have fewer. This is mainly due to asynchronous approval in different countries, which may result in patients not having appropriate access to drugs. The delays in regional approval decisions, the lack of availability of certain drugs, and delays in either prescription or access to drugs breach the ethical principles of fairness and justice for patients with PAH or CTEPH in Latin America. We believe that these issues must be highlighted by Latin American scientific and academic societies to improve and provide more rapid access to essential therapeutic strategies for patients across the region. These meetings should be supported by non-Latin American physicians and patients or advocates, which may help address and provide expert recommendations on this area specifically for the region and patient/family insights on the problem.

CONCLUSIONS

In general, current clinical practice in Latin American countries is imprecise and processes must be aligned. In Latin America, this is the result of a multifactorial problem in which each country has different access to medications and care based on individual health systems, wealth, and geographic access. We believe that the practical experiences of physicians from the participating countries should be considered of high intrinsic value, as they describe a uniquely Latin American reality. By disseminating these experiences among healthcare professionals and stakeholders such as health institutions administrators and payers, the impact of these experiences on everyday clinical practice can be increased.

ACKNOWLEDGMENTS

Medical writing assistance was provided by Dr. Ana Maria Perez, funded by Bayer South America, Bogota, Colombia in accordance with Good Publications Practice (GPP3) guidelines.

CONFLICT OF INTERESTS

Dr. Orozco-Levi is the inventor of 14 medical devices, none of them related to the present manuscript; he declares no relationship with the tobacco industry; he is the Head of the EMICON group, which has received research grants from MINCIENCIAS-Colombia; he is codirector of the Colombian Network of Pulmonary Hypertension (HAPred.co); and he has participated in advisory boards and received consulting and/or lecture fees from Bayer, Actelion/Janssen, Pint-Pharma, and Abbott. Dr. Cáneva has received speaker fees from Actelion, Bayer, Bagó, and Tuteur, participated on advisory boards for Bayer, Actelion/Janssen, received financial support for participating in medical congresses from Bayer, GlaxoSmithKline, Actelion, and Tuteur, and has been the principal investigator on clinical trials supported by Actelion, Bayer, United Therapeutics and Lung Therapeutics. Dr. Fernandes received fees for lectures and participating in Advisory Boards from Bayer and Janssen. Dr. Restrepo-Jaramillo has received personal fees from Bayer for a Speaker's Bureau. Dr. Zayas has participated in advisory boards and paid lectures for Actelion/Janssen, Bayer, and

Ferrer. Dr. Conde has received sponsorship from GlaxoSmithKline, Actelion/Janssen-Cilag, Pint pharm, Ferrer International, and Bayer South America for academic and consulting activities. Dr. Diez has nothing to disclose. Dr. Jardim received speaker fees from Actelion and Bayer and for participation in advisory boards from Janssen and Bayer. Dr. Pacheco Gallego has nothing to disclose. Dr. Melatini has received speaker fees from Bayer and Janssen and has received funding from Bagó for data registration and medical research. Dr. Valdez has nothing to disclose. Dr. Pulido has participated in advisory boards and paid lectures for Actelion/Janssen, Bayer, Pfizer, Ferrer, and GlaxoSmithKline. His institution has received research grants from Actelion/Janssen, Bayer, REATA, and United Therapeutics.

ETHICS STATEMENT

Ethics statement is not applicable to this study.

AUTHOR CONTRIBUTIONS

M. Orozco-Levi is responsible for the overall content of the manuscript. All authors contributed to the drafting and critical revision of their respective geographical sections of the manuscript. All authors approved the manuscript for submission.

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How to cite this article: Orozco-Levi M, Cáneva J, Fernandes C, Restrepo-Jaramillo R, Zayas N, Conde R, Diez M, Jardim C, Pacheco Gallego MC, Melatini L, Valdéz H, Pulido T. Differences in health policies for drug availability in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension across Latin America. Pulm Circ. 2022;12:e12012. https://doi.org/10.1002/pul2.12012