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GLOBAL PRACTICE OF SLEEP MEDICINE

Past, present, and future of sleep medicine research in Latin America

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Sleep medicine is a relatively young field with exponential growth in development and research in the last decades. Parallel to the advances in the United States, Latin America also had its beginnings in sleep medicine housed in neuroscience laboratories. Since the very first Latin American meeting in 1985, and the first sleep society in 1993, sleep research has undergone significant development in subsequent years. From contributions in animal research that allowed understanding of the activity of the brain during sleep to the studies that improved our knowledge of sleep disorders in humans, Latin America has become a scientific hub for expansion of sleep research. In this article, we present a historical account of the development of sleep medicine in Latin America, the current state of education and the achievements in research throughout history, and the latest advances in the trending areas of sleep science and medicine. These findings were presented during World Sleep Society meeting in Vancouver in 2019 and complement the work on sleep societies and training published by Vizcarra-Escobar et al in their article "Sleep societies and sleep training programs in Latin America" (*J Clin Sleep Med*. 2020;16(6):983–988).

Keywords: sleep, Latin America research, future research perspectives, recent advances

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INTRODUCTION

Latin America similarly to the rest of the world initiated research in sleep medicine from basic neurosciences. Technological advances and the advent of electrophysiology gave a global boost to define the behavior of the cerebral cortex and to help identify sleep stages. We consider the 1960s a starting point for sleep research in Latin America. Countries with established research institutes in other scientific fields led the initial sleep research in basic and clinical areas. It is important to highlight that this process grew in parallel to Europe and the United States.

Considering the countries with established basic research as leaders in sleep research, we will start our survey by presenting the main players who laid the research foundations for the development of sleep medicine in the rest of Latin America. These countries also have the largest number of publications per million inhabitants (**Figure 1**). We will continue by discussing current areas of research and end by proposing future opportunities for research in sleep medicine.

HISTORICAL PERSPECTIVES: THE BEGINNINGS OF SLEEP MEDICINE IN LATIN AMERICA

The Latin American Sleep Society was created in 1986.[1] After the first eight congresses, it was decided to change the name to Federation of Latin American Sleep Societies, during the World Federation Sleep Research Societies congress held in Uruguay in 2001. One of the main objectives during this meeting was to promote the development of sleep medicine in all Latin American countries. Thus, the societies of Peru, Ecuador, and Colombia were formed and integrated. In 2009, Brazil organized the World Association of Sleep Medicine international congress. The Latin American sleep community managed to hold congresses without interruption every 2 years, adding new societies in different countries (**Table 1**).

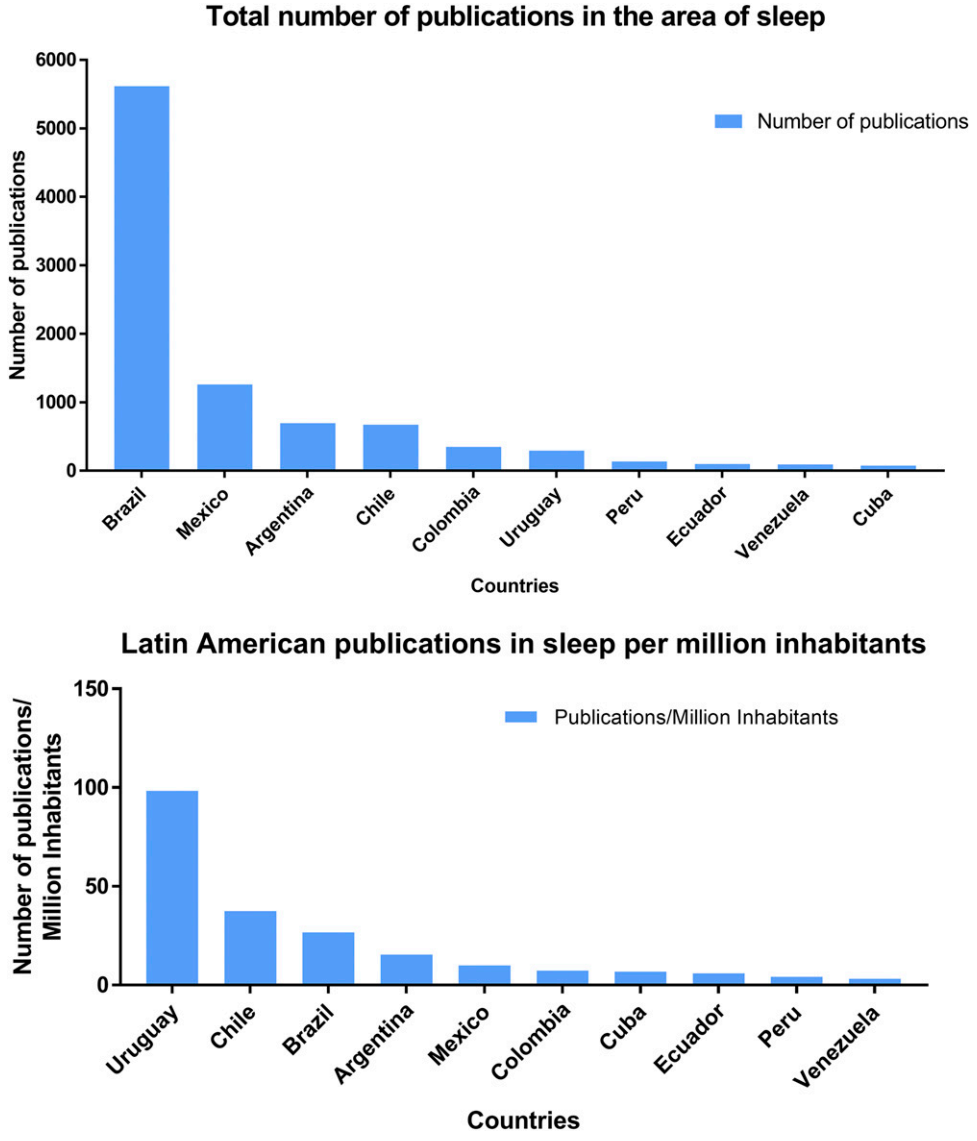
Mexico

Mexico exemplifies one of the counties with establish researchers, particularly Ruy Pérez Tamayo,[2] a medical pathologist and immunologist, and Augusto Fernandez Guardiola (1921–2004),[3,4] a neurophysiologist and neuropsychiatrist with important research in neuroscience and epilepsy. These leading researchers promoted the creation of neuroscience research institutes in Mexico. In the 1950s and 1960s important original sleep research began to grow in the hands of 2 prominent figures: Raúl Hernández Peón (1924–1968), who investigated the mechanisms that underlay rapid-eye movement sleep,[5] exploring the actions of acetylcholine in the brainstem with crystal microinjections[6]; and René Drucker Colin (1937–2017), with studies of sensory and motor systems and sleep.[7] With these pillars, sleep research and, later, the field of sleep medicine began to be built. Sleep centers first emerged from academic institutions, then they appeared in hospitals with interdisciplinary approaches.

Brazil

In Brazil, the 3 pillars contributed a framework for neuroscientific thinking and began sleep research were Miguel Rolando Covian (1913–1992), Cesar Timo-Iaria (1925–2005), and more recently—giving continuity to the processes of growth—Sergio

Figure 1—Countries with the highest number of publications per million inhabitants in the field of sleep in Latin America.



Tufik. As pointed out by a historical review by Miranda and colleagues (2016)[8], studies from Drs. Covian and Timo-Iaria covered a wide array of subjects, including neural regulation of the digestive system and electrical activity of the brain. Together with Katsumasa Hoshino, Cesar Timo-Iaria was responsible for great advances concerning the use of animal models for the investigation of electroencephalographic hallmarks of sleep.[9] Sergio Tufik engaged in studies on the effects of centrally acting agents on the sleep-wake cycle, identifying the effects of sleep deprivation on the dopaminergic system, which caused a supersensitivity in its receptors.[10] He was also responsible for large-scale epidemiological studies assessing the sleep quality of the general population in the city of São Paulo. In this way the discipline of sleep medicine emerged with all its branches, from basic research in animal models to clinical research. Brazil had its first sleep congress in 1985 and formed its first sleep society in 1993 with a congress every 2 years. Brazil has 8 regionals societies all around the country with about 500 certified professionals (technicians and doctors) and more than a thousand sleep laboratories. Their societies offer support, controls, and certification commissions. Since 2000 they have elaborated a consensus and guidelines for sleep disorders and pathologies. All this has been achieved thanks to a clear and comprehensive vision of the path to be traveled. An example of this is what the Sleep Institute founded by Sergio Tufik says in the description of its premises:

> *Founded in 1992 by doctors from the São Paulo School of Medicine (UNIFESP), its main mission is to carry out pioneering research, trying to understand mainly the basic mechanisms of sleep and its possible applications in the clinical area (diagnosis and treatment). Scientific research is the flagship of the institute's activities, but it also offers courses for graduate and post-graduate students and for polysomnography technicians.*

Thus, they have for decades been carrying out high-level research, sleep medicine with clinical and paraclinical care for patients, and training in human resources.

Table 1—Latin America sleep congresses.

Year	Country	Edition	Association
1986	Brazil	I	LASS
1988	Argentina	II	LASS
1990	Uruguay	III	LASS
1992	Mexico	IV	LASS
1994	Chile	V	LASS
1996	Colombia	VI	LASS
1998	Argentina	VII	LASS
2000	Brazil	VIII	LASS
2001	Uruguay	Sleep Odyssey	WFSRS
2002	Mexico	IX	FLASS
2004	Uruguay	X	FLASS
2006	Chile	XI	FLASS
2008	Peru	XII	FLASS
2009	Brazil		WASM
2010	Ecuador	XIII	FLASS
2012	Colombia	XIV	FLASS
2014	Mexico	XV	FLASS
2016	Colombia	XVI	FLASS
2018	Uruguay	XVII	FLASS

FLASS = Latin American Federation of Sleep Societies, LASS = Latin American Sleep Society, WASM = World Association of Sleep Medicine, WFSRS = World Federation of Sleep Research Societies.

Uruguay

Uruguay has had in the 20th century important developments in the area of neurosciences that began with the foundation of the Institute of Neurology of the Hospital de Clínicas of Montevideo. In this environment the first research in sleep medicine was generated. One of the first scientific reports relating an injury to changes in the behavior of the sleep-wake cycle was from Dr. Francisco Soca from Uruguay, who in 1900 described a young patient with a tumor localized over the sella túrcica that was found compressing the anterior hypothalamus and presenting clinically with continuous and prolonged sleep.[11] This description was 30 years before Von Economo (1930) proposed the anterior hypothalamus as a sleep facilitatory area. However, systematized sleep research began with Elio García-Austt,[12] who worked on sensory systems, temporal processing, and biological rhythms, publishing in 1963 the first mention in the medical literature of a change in a sensory response during the transition from wakefulness to slow sleep.[13–16] In the 1970s García Austt went to Spain fleeing the military dictatorship that lasted 11 years in Uruguay, and he founded there the Spanish Society of Neuroscience with Reinoso Suárez. However, the continuity in the development of sleep research was maintained thanks to Ricardo Velluti (1937–) and Jaime Monti (1934–), who remained in the country and developed a basic research laboratory and a clinical and pharmacological laboratory of sleep, respectively. Two books can summarize Velluti's scientific trajectory: He published, together with Pier Luigi Parmeggiani, a basic book of sleep physiology (2005)[17] and a book about his main expertise, auditory processing during sleep (first edition in 2011, reissued in 2018). Together, Drs. Velluti and Monti investigated the pharmacology of sleep and the effects of psychotropic drugs in the sleep-wake cycle (Monti and Velluti, 1974).[18] Both were prominent figures in the development and expansion of sleep science and medicine in Uruguay.

Argentina

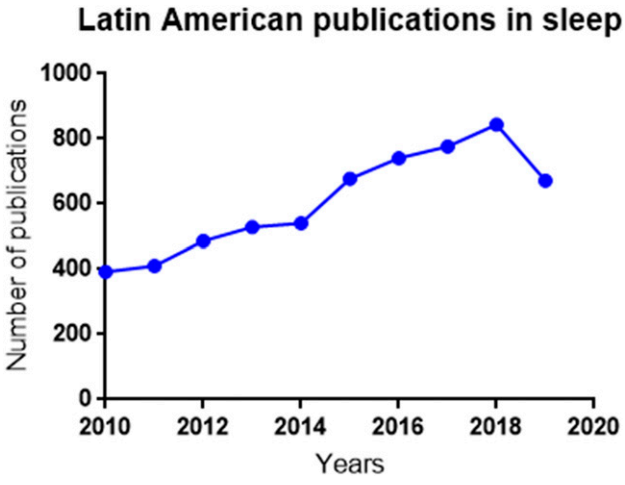
Dr. Daniel Cardinali is a leader in sleep and chronobiology research. With more than 600 publications he has advanced research on the characteristics and utilities of melatonin,[19,20]

Regarding the clinical sleep laboratory, Dr. Horacio Encabo[21] began as a basic electrophysiology researcher (1984) and opened the first sleep laboratory in Argentina at the FLENI (Fundacion de Lucha contra las Enfermedades Neurologicas Infantiles) Clinic. Margarita Blanco (1949–2004) led a survey of sleep disturbances in 3 Latin American countries.[22]

Chile

Chile has also had important figures and groups in neuroscience since the early decades of the 20th century. The most prominent was Joaquín Luco (1913–2002).[23,24] Although his research was related to factors affecting memory, he was instrumental in the establishment of neuroscience research institutes. Dr. Patricio Peirano led research in sleep with several publications since the 1980s concerning sleep and metabolism.[25] Further research on Sudden Infant Death Syndrome has been conducted by investigators from the Universidad Catolica de Chile. Several publications on

Figure 2—Number of publications in the topic of sleep in the past 10 years, considering the 10 most prolific countries in Latin America.



obstructive sleep apnea (OSA) in children have emerged from that group.[26] Bertrand led early studies on airway endoscopy in patients with Down syndrome.[27] The same group published early studies on polysomnographic findings in infants with gastroesophageal reflux.[28]

NOVEL FINDINGS IN TRENDING TOPICS: LATIN AMERICA TODAY

Research and publications

It is difficult to know the exact number of publications in the area of sleep to which Latin-American scientists have contributed, mainly because participation of researchers from Latin America is not limited to efforts produced exclusively in their respective countries but include international collaborations. In this sense, the following data and numbers take into consideration not only studies performed in Latin America but also the numerous collaborations performed in past years with centers around the world. As of 2019, Web of Science lists a total of 8943 sleep-related articles from the 10 most prolific Latin-American countries in this field area (**Figure 1**), of which 668 are from the 2019 (**Figure 2**). Considering the same countries, in SCOPUS (Elsevier, Amsterdam), 9,322 documents related to the keyword "sleep" can be found, with 2019 accounting for 688 of these publications. These numbers express not only the sheer amount of scientific production in the field of sleep but how the breadth of research and its significance has advanced in recent years.

Regarding highly cited articles in the past 10 years, it must be noted that many of the most prominent studies are of a clinical nature, focusing on the evaluation of sleep disorders and their epidemiological aspects. In this sense, notable contributions to the understanding and treatment of OSA have been made. In a study performed by Pedrosa and colleagues (2011)[29], OSA was established as the most common secondary cause of hypertension in the subpopulation of patients with resistant hypertension. Another significant study found that the prevalence of OSA in a large, representative sample was 32.9%, a value that put into discussion the previous general belief that OSA prevalence in the general population would not exceed 8%.[30] A Brazilian group has been involved in a population-based study composed of a representative sample of the population of São Paulo, Brazil, named EPISONO (Sao Paulo Epidemiologic Sleep Study). This study aimed to describe the prevalence of sleep disorders and its association with multiple outcomes.[30] More than 60 articles have brought to attention the prevalence of several sleep disorders as well as their association with overall outcomes and pathophysiological mechanisms.

The achievements of Latin-American researchers, however, spread out further, with relevant collaborations performed by research groups worldwide that have made significant contributions to scientific knowledge. Among these are contributions to the treatment for sleep disorders and its benefits for cardiovascular outcomes[31] and the updating and extensive revision of the body of evidence concerning the uses of melatonin and the findings of chronobiological studies[32] must be remembered. Latin-American sleep scientists have also participated in the investigation of the effects of cannabinoids in sleep and its possible uses and implications in the clinical scenario.[33]

It is clear that the role of the sleep societies in Latin America is relevant, with a prominent focus on the study of sleep disorders and on chronobiological regulation of sleep. These topics, alongside other trends observed in the field of sleep medicine, can be listed as crucial areas of interest for sleep science and medicine worldwide.

Sleep disorders and comorbidities: advances in the understanding of associated conditions

The relationship of sleep disturbances and their comorbidities has been the focus of study since the beginnings of sleep research, and in modern times, it is still of great importance. Particularly, obesity and cardiovascular conditions are 2 of the main concerns in sleep medicine currently, due to the already well established connection between these factors and sleep disorders and the clinically relevant outcomes that may appear. Identification of factors and contributors that link sleep to such problems is one of the main priorities. A study by Carneiro and Zanella (2018)[34] highlighted the bidirectional characteristics of the relationship between OSA and obesity, constituting a vicious cycle in which both conditions contribute to the maintenance or aggravation of the other. This article also brings attention to the increased risk for cardiovascular events and the need for changes in lifestyle of patients with both conditions. Considering this, a large focus has been given to the relationship between sleep apnea, obesity, and cardiovascular events. Recently, a study assessing data collected from the EPISONO cohort has highlighted the importance of physical activity as a protective factor against metabolic risk and development of OSA. It is among the first prospective studies evaluating a probabilistic sample regarding the relationship between physical activity, sleep apnea, and cardiometabolic risks.[35]

Going beyond OSA, progress can be seen in the characterization of type-1 and type-2 narcolepsy in a recently published

study (Cremaschi et al, 2019)[36]. In this report, evaluation of chronic pain has shown that patients with either subtype of narcolepsy have significantly more intense pain compared to controls. Of note, this is the first study reporting chronic pain as a comorbidity of type-2 narcolepsy. It must be highlighted that obese patients with narcolepsy did not differ with respect to their pain levels from obese controls.

Here, we have addressed only a handful of examples that show how the study of comorbidities of sleep disorders has been a widely explored field of research, and how the Latin-American sleep scientific community has been decisive in expanding the findings on this area. It can be said that there is still a large portion of this field that can be explored. As an example, the relationship between sleep and neurodegenerative conditions has become a point of great interest, not only for understanding sleep but for the many implications these diseases have for general health and because of their increase in prevalence as a possible consequence of the aging of the general population.

Sleep and neurodegeneration: the role in Alzheimer and Parkinson diseases

As of today, the connection between sleep and neurodegenerative diseases is well established. Due to recent advances, such as the description of the glymphatic system by Iliff and colleagues (2012),[37] current knowledge of this link has undergone expansion, with the result that studying the bidirectional relationship has become an accepted and a promising field of research. The glymphatic system is a mechanism of metabolite clearance of the brain that becomes active during sleep. Poor sleep may contribute to its malfunctioning and consequently led to accumulation of harmful metabolites such as tau-protein and formation of neurofibrillary tangles associated with Alzheimer disease. Therefore, the glymphatic system constitutes a field of necessary research in which our sleep societies may play a role in the future.

In this regard, progress in the understanding of the relationship between neurodegenerative conditions and sleep has been achieved by Latin-American researchers. A recent study by Ehrenberg and colleagues (2018),[38] led by Dr. Lea Grinberg, has shown that specific stages of Alzheimer disease development may be connected to the appearance of sleep disorders. Postmortem analyses and interviews with relatives have shown that sleep disturbances increased in patients who had a Braak scale of neurofibrillary tangle burden of I/II.

Besides Alzheimer disease, great effort has been expended in trying to understand the mechanisms and associated comorbidities of Parkinson disease (PD). Studies linking sleep and PD tend to focus on investigating REM Sleep Behavior Disorder, which is considered a prodromal marker for this disease. However, Latin American studies have been exploring different aspects of the condition. Among the latest research, we must highlight efforts to identify a link between Parkinson and comorbid impulse control disorder,[39] a goal that has been eluding scientists in recent attempts. Additionally, insights into the anatomical changes influencing Parkinson and sleep disorder have been made, with identification of laryngopharyngeal motor dysfunction as a contributor to obstructive sleep apnea in patients with Parkinson.[40] Pharmacological treatment of Parkinson, which relies mainly on dopaminergic agonists, has also been a focus of attention, with daytime consequences being connected to them. Finally, clues to the usefulness of melatonin as therapy for neurodegeneration have warranted further investigation of this molecule. Taken together, these updates highlight the importance of the participation of Latin-American sleep scientists to an improved understanding of neurodegenerative conditions and thus to clinical advances in their treatment.

Sleep in a chronobiological perspective: contributions in the study of melatonin

The importance and possible uses of melatonin to ameliorate a number of health conditions is one of the main trends observed not only in sleep medicine but in clinical research as a whole. As pointed out by Cardinali,[41] melatonin warranted investigation of its possibly beneficial effects on neurodegenerative and oxidative processes and as such has been thoroughly investigated for these purposes lately, highlighting that, besides its antioxidant properties, melatonin acts as a chronobiotic, antifibrillogenic, and cytoskeletal agent. Melatonin would be a possible countermeasure to the progression of Alzheimer and Parkinson diseases, with marked effects if used in their early stages.[42] Thus, investigation of the mechanisms by which endogenous melatonin is affected by different factors is essential. A recent work provided considerations about environmental factors that may regulate melatonin levels. Availability of oxygen has been proven to play a role in melatonin production: hypoxic conditions led volunteers to present higher levels of the hormone, with a delayed diurnal remission on melatonin levels. This may suggest a decrease in the organism sensitivity to melatonin in hypoxic conditions.[43] Genetic factors that influence secretion of melatonin and its link to individual characteristics also warrant investigation, with possible clinical implications to be found. Another study has identified that a polymorphism in melatonin receptor 1B may be related to an extreme morningness chronotype and modulation of sleep habits, thus providing the first insights into the role of this gene in sleep regulation and rhythm synchronization.[44]

Sleep in our society: epidemiological studies in Latin America

In the context of epidemiological evaluations of sleep in Latin America, some particularities must be considered. Latin-American countries may present subpopulations that differ in several ways from populations customarily assessed and who thus deserve special attention. As an example, Del Brutto and colleagues (2017)[45] performed a cohort study, the Atahualpa Project, that focused on evaluating sleep in a rural community in the Ecuadorean countryside. This effort is particularly important due to the higher exposure of the cohort to outdoor environments—and consequently to the effect of sunlight in rural populations—a condition that still predominates for a large portion of the inhabitants of Latin America. Moreover, in this study, application of the Epworth and Berlin questionnaire yielded poor correlations with other variables investigated. These findings may result from the difficulty of the local

population to relate to the questions and put into discussion the need for creating tools that may be adequate to assess sleep in specific populations.

Considering urban populations, the fourth edition of the EPISONO cohort study, which evaluates sleep quality and several related health parameters in the population of São Paulo, has recently concluded. This large-scale research may present another view regarding evaluation of sleep in Latin-American populations. First, it will be possible to investigate the evolution of sleep complaints in a representative sample from the largest urban center in the Southern Hemisphere by performing comparisons with the findings from the previous editions of the study. The EPISONO study will also allow comparisons of the prevalence of different sleep disorders and associated comorbidities with data from other large cities around the globe. Therefore, it may contribute to the understanding of patterns of sleep quality in urban scenarios and highlight possible differences between these same urban centers according to location, social factors, and populations characteristics.

CONSIDERATIONS ABOUT THE FUTURE: CHALLENGES AND STRENGTHS

While the exposition performed in the present review highlights the expansion and establishment of Latin-American sleep research, it is not possible to discuss its future without looking to the current social, political, and economic conditions that countries on this continent have faced in past years. One of the most significant concerns has been governmental support of research. Budget-cutting policies in Mexico, Brazil, and Argentina, the 3 countries with the largest output in sleep science, are menacing the continuity of research in several areas. The sanction of financial support for research comes with the prerogative of stabilizing economies after financial crises that began in previous terms. However, one must note that investment in science and technology are one of the main pathways to resolving a crisis and do not constitute a secondary expense. Considering this, it is necessary that the scientific community around Latin-American countries work together to preserve their integrity and ask for support from responsible state-owned entities.

Another point of concern that is commonly associated with the decrease in governmental investment in science is the lack of interest by and information among the general population of Latin-American countries regarding scientific processes. It has become evident in recent years that one of the main challenges to be faced may be reaching out to those outside the scientific community. Currently, as shown in several occasions by the media, a sizable part of the population does not have knowledge of science and the work of a researcher. In some cases, science is perceived as harmful and biased, points that demonstrate how urgently we must improve our communication with society. Therefore, besides expansion and maintenance of the output shown in past years, Latin-American sleep science must also address a reduction in research funding and the lack of knowledge about scientific research and its importance among the populations of these countries.

FINAL THOUGHTS

The present review emphasizes the substantial advances the area of sleep science and medicine has experienced in past years in Latin America. With great capacity for innovation, significant collaborations with research groups worldwide, and ubiquity in the topics that have been the main focus of interest in sleep research, Latin America has established itself as a scientific hub with potential for further growth and a promising future.

However, it must not be forgotten that currently many challenges to growth in sleep medicine and science have surfaced, including the loss of governmental funding and of support by the population. These factors may jeopardize not only the development of sleep science but every field of scientific research in Latin American countries. Therefore, besides maintaining its growth in scientific research and its contributions to sleep science and medicine worldwide, sleep societies in Latin America must bridge the gap linking scientific production and their populations and take a position in relation to reductions in research funding that have been affecting many of their countries. Given the essential role scientific research has in the improvement of the conditions of society, in all of its aspects, ensuring the integrity of scientific research and reaffirming its importance is mandatory for progress of Latin America as a whole.

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