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Strategic Opportunities in Sleep and Circadian Research: Report of the Joint Task Force of the Sleep Research Society and American Academy of Sleep Medicine

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EXECUTIVE SUMMARY

Sleep and circadian timing are fundamental biological imperatives in animals and humans, throughout the lifespan. These biological systems can be challenged by pathology, individual choices, and social/societal pressures, often resulting in sleep loss or circadian disruption (i.e., "sleep deficiency"), and ultimately adverse health and safety outcomes. Advances in the scientific knowledge generated during the last decade indicate the transformative potential of sleep and circadian health for improving the health of the American people, including the development of novel, personalized, preventative and therapeutic strategies for multiple chronic diseases. The American Academy of Sleep Medicine (AASM) and the Sleep Research Society (SRS) created a Task Force with a mandate to engage the sleep and circadian scientific community, the National Institutes of Health (NIH) and other key stakeholders to help catalyze the implementation of the most time-sensitive research priorities identified in the 2011 NIH Sleep Disorders Research Plan.

Given the mounting evidence of the importance of sleep health to overall physical health, behavioral health and safety, together with the rapid advances in basic sleep and circadian science, we need to seize on this opportunity to accelerate translational and clinical research in sleep and circadian rhythms. This white paper represents the proceedings and consensus development at the Joint Task Force on Sleep and Circadian Research Conference held in 2013 in Bethesda, MD. It is directed toward all invested in sleep and circadian research for their consideration, including researchers, educators, patients, professional societies, industry partners, funding-decision and policy makers. This documentation is timely and comes on the heels of a compelling call for an international effort in this area.[1] The four major research goals and specific recommendations for each of these goals were identified. These recommendations can be adapted and directed to prioritize research in various populations and clinical settings.

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Goal 1: Address the health and societal impact of sleep deficiency and circadian dysfunction.

Recommendations:

- Support basic and translational research to identify causal and interacting relationships and mechanisms underlying the impact of sleep deficiency on health throughout the lifespan.
- Develop tools and biomarkers to assess sleep quality and circadian function, including molecular, cellular, and physiological signals.
- Identify the genetic variants that predispose to variations of sleep/circadian rhythms and sleep-wake disorders, as well as vulnerability to the effects of sleep loss on behavior, cognition, and health.
- Investigate the differential vulnerability to sleep deficiency and its adverse consequences with respect to maturational stage, clinical and societal factors such as chronic illness, health disparities due to social, demographic, environmental, and geographic attributes, and health inequalities secondary to racial, ethnic, socioeconomic, or educational attributes.
- Establish normative age- and gender-specific data for sleep duration, sleep quality and circadian timing using both self-reported and objective sleep and circadian phenotyping in studies that include analysis of diverse ethnic and socioeconomic groups.
- Design and evaluate intervention strategies assessing the wellness impact of improved sleep and circadian alignment on physiological functioning, behavior, health, and well-being throughout the lifespan.

Goal 2: Develop new approaches to improve treatment outcomes for sleep and circadian disorders and to address this in the context of personalized patient-centered care and healthcare disparities.

Recommendations:

- The AASM, SRS, and other professional societies and patient organizations should work collaboratively to identify and validate relevant patient-centered outcomes that can be incorporated into clinical practice.
- Partner with insurers and vendors of electronic medical records to integrate relevant information and outcome

measures for common sleep disorders into electronic medical records.
- Investigate and reduce the impact of chronic disease, healthcare disparity, and inequality on sleep and circadian disorders.
- Promote the development of personalized sleep/circadian medicine through the identification and validation of individualized approaches to the management of sleep and circadian disorders.
- Support basic science research for developing new ways of understanding sleep and circadian disorders at a basic mechanistic level to generate new approaches to their diagnosis and treatment.
- Support research to determine if sleep deficiency/sleep disorders represent modifiable risk factors that can alter the expression and course of chronic diseases.

Goal 3: Establish research networks and informatics infrastructure.

Recommendations:
- Support the development of specialized infrastructure for clinical research in sleep and circadian disorders, including the establishment of disease registries, national core laboratories, and clinical research networks.
- Promote the utilization of open source data and tools resources across sites to maximize data sharing and standardization.
- Establish appropriate governance of networks to ensure they are responsive to the needs of the field of sleep and circadian research broadly, and that they are sustainable.

Goal 4: Enhance sleep and circadian research training.

Recommendations:
- Expand T32 grants to Institutes beyond the NHLBI and explore adding slots to existing T32s in areas such as genomics, systems biology, translational/patient-oriented research and patient-centered outcomes research.
- Develop additional T32 multi-institutional training grants in areas relevant to the Strategic Plan for sleep and circadian research.
- Develop electives and resources focused on sleep and circadian health and sleep and circadian physiology for use by professional programs including, but not limited to, medical schools (allopathic and osteopathic), graduate nursing programs, clinical psychology, dental schools, and physician assistant schools.
- Attract researchers in other fields to address important sleep related research questions through engagement in collaborative research on proposals and encourage the development of innovative mechanisms for interdisciplinary training programs.

INTRODUCTION

Sleep and circadian rhythms influence nearly all molecular, cellular, physiological, and neurobehavioral processes. Sleep deficiency and sleep and circadian disorders affect 50 to 70 million Americans with wide ranging consequences for health and safety.[2] Phenotypic expression and treatment of numerous medical, neurological and psychiatric disorders is influenced by sleep deficiency. Sleep disorders disproportionately burden disadvantaged populations, underscoring their public health importance and potential to address health disparities in our society. The direct and indirect economic burden to the country is estimated to be in the many billions of dollars. Scientific knowledge generated from this rapidly emerging field has transformative potential, and provides an opportunity for new directions toward improving the health of Americans and worldwide, including the development of novel, personalized treatments of the chronic diseases.

The Sleep Research Society (SRS) and American Academy of Sleep Medicine (AASM) created a Joint Task Force to help advance the national sleep research agenda as outlined in the 2011 NIH Sleep Disorders Research Plan.[3] This white paper represents the proceedings and consensus development at the Joint Task Force on Sleep and Circadian Research Conference held in 2013 in Bethesda, MD. Participants included Joint Task Force members, representatives of the Trans NIH Sleep Coordinating Committee, Sleep Disorders Research Advisory Board (SDRAB) and National Center for Sleep Disorders Research (NCSDR), as well as sleep and circadian researchers from the community. The goal of the conference was to develop strategies to implement the opportunities identified in the NIH Sleep Disorders Research Plan. The four major transformative opportunities identified were: (1) to address health and societal impacts of sleep deficiency (insufficient sleep duration and/or sleep quality) and circadian dysfunction; (2) to develop new approaches to improve the outcomes of treatment of sleep and circadian disorders and to address outcomes in the context of personalized patient-centered care and healthcare disparities; (3) to implement research networks and big data informatics to support sleep and circadian research and to serve as engines of innovation; and (4) to train the future generation of sleep and circadian researchers, particularly in the advanced and novel scientific approaches that will be required.

As the 2011 NIH Sleep Disorders Research Plan is intended to be a "living" document, stakeholders should frequently review the Plan's recommendations and, if needed, offer further direction about specific research needs or opportunities. This document serves this purpose at this time and is directed toward all invested in sleep and circadian research for their consideration, including researchers, educators, patients, professional societies, industry partners, funding decision and policy makers.

It is our intention to move these recommendations into the implementation phase by encouraging exchange of ideas, partnerships and advances in these identified goal areas by stakeholders. Some of the recommendations can be implemented by the Sleep Research Society and/or American Academy of Sleep Medicine, others can be stimulated by the organizations including providing seed resources, while others will require collaboration with federal agencies. Ultimately, it will require the creative talent of individual investigators or teams of investigators to make the vision laid out in this document a reality. Ongoing efforts to maintain transparency and regular communication between the Sleep Research Society, the American Academy of Sleep Medicine, and the stakeholders will be important in this regard.

HEALTH AND SOCIETAL IMPACT OF SLEEP DEFICIENCY AND CIRCADIAN DISTURBANCE

Background

Sleep deficiency is highly prevalent whether due to sleep disorders, insufficient sleep, inadequate sleep quality or circadian misalignment. One-third of adult Americans and up to 70% of high school adolescents obtain less than 7 hours of sleep per night,[4,5] with the prevalence of curtailed sleep duration increasingly affecting even the youngest of children.[6,7] One-fifth of the US workforce is engaged in shift work,[8] putting them at risk for both sleep deficiency and circadian misalignment. Appreciation of the prevalence of unhealthy sleep, as well as the importance of healthy sleep, has prompted the recognition of "sleep health" as a national priority in the Healthy People 2020 program.[9] This program influences US federal funding priorities and indirectly affects state and local funding for programs through mandates tied to meeting Healthy People 2020 goals. Presently, the significance of healthy sleep remains under-recognized by policy makers, the health care community, and the public at large, despite compelling evidence of its critical importance.

There are many biological factors, individual behaviors, and societal and economic pressures that result in insufficient sleep duration, inadequate sleep quality, and/or sleep disorders. These factors often co-occur, and frequently have similar adverse outcomes. For this reason, the term "sleep deficiency" provides an overarching operational concept that helps capture this overlap in a way that can facilitate policy decisions, community-based interventions, and public education campaigns.

Sleep deficiency reflects sleep that fails to meet physiologic need, usually through short sleep duration or inadequate sleep quality.[10] Short sleep duration (often arbitrarily defined as 6 hours or less on average per night in adults) is estimated to be experienced by 25% to 35% of the US adult population. For example, data from the 2004-2007 National Health Interview Survey[11] and the 2009 Behavioral Risk Factor Surveillance System both estimate the prevalence of short sleep at 35%.[12] The prevalence of sleep deficiency in children is unclear, since even healthy children are objectively sleeping less than previously estimated.[13]

"Inadequate sleep quality" affects 18.8% of American adults and refers to sleep that, regardless of duration, is characterized by the impaired ability to initiate sleep, frequent and/or extended interruptions of sleep or the experience of non-restorative sleep.[14] The most common cause of inadequate sleep quality are sleep disorders that disrupt normal sleep and circadian processes (e.g., insomnia disorder, obstructive sleep apnea, restless legs syndrome, circadian rhythm sleep-wake disorders, parasomnias and narcolepsy).[15] Among these disorders, the most prevalent are insomnia and sleep apnea, which are estimated to respectively affect 10% to 20% and 5% to 15% of the population.[16,17] Moreover, racial and ethnic differences in sleep duration may exist and that may in turn confer or mediate cardio-metabolic risk. For example, African Americans have higher rates of extreme sleep durations (long and short) than their Caucasian counterparts, which, may in turn, mediate a higher risk of cardiovascular disease, obesity, and diabetes among African Americans.[18] Chronic sleep and wake disturbance can also result from disruption of internal circadian timing or misalignment between the individual's circadian rhythm of sleep-wake propensity and the 24-hour social and physical environments. Many individuals experience chronic circadian misalignment due to shift work (where individuals' opportunity for sleep falls outside of the optimal physiologic time for sleep),[19] circadian rhythm disorders (e.g., advanced or delayed sleep phase),[20] transmeridian travel,[21] or irregular social schedules.[22]

Sleep deficiency is associated with significant adverse outcomes for safety and health. A major public safety concern is the impact of sleep deficiency on motor vehicle and workplace accidents. According to the National Highway Traffic Safety Administration (NHTSA), drowsy drivers were involved in 2% of all non-fatal crashes and in 2.5% of fatal crashes in 2009.[23] This is not surprising if one considers that 4.2% of drivers report having fallen asleep while driving during the previous month according to the Behavioral Risk Factor Surveillance System (BRFSS). Reports of falling asleep while driving were more common among adults who reported short sleep time, snoring, or unintentionally falling asleep during the day compared to other adults who did not report these issues.[24]

Experimental sleep deficiency has been shown to increase established risk markers for cardio-metabolic disease, including markers of systemic inflammation, dysregulation of appetite regulating hormones, weight gain, impaired glucose tolerance, and decreased insulin sensitivity.[13,25-27] These physiological responses to insufficient sleep and other factors may be responsible for the observed relationship between increased weight gain and obesity, as well as increased risk of diabetes, hypertension, dyslipidemia, and other cardiovascular and metabolic disorders, as well as cognitive, behavioral and mood alterations associated with sleep deficiency in population studies.

While translational studies are of great importance, there is a need to strengthen the basic science underpinnings of this effort. New animal models in multiple species are needed to study the consequences of sleep deficiency at molecular and cellular levels. Given the increasing prevalence of shift work and jet lag, and their behavioral and physiological consequences, studies of circadian misalignment are of obvious import. Understanding the functions of sleep and the interaction between the brain and peripheral organs are essential to fully elucidate how to address sleep deficiency.

Opportunities and Needs

The substantial evidence linking sleep deficiency with adverse health and safety consequences demands that healthy sleep and circadian function be defined in the general population to improve behavioral and physical health and well-being. Moreover, particular attention is needed to define sleep and circadian health for diverse age groups, ethnic groups, and in society's most socioeconomically disadvantaged, as they are more likely to engage in shift work and are more likely to have extreme (long and short) sleep durations and experience poor sleep quality. Understanding the genetic, epigenetic bases and biological mechanisms of differential sleep need, and vulnerability to adverse consequences of sleep deficiency is a major concern for our field and will be the focus of research at all levels from bench to public awareness, in the coming years.

Recommendations:

1. Support basic through translational research to identify causal and interacting relationships and mechanisms underlying the impact of sleep deficiency on medical, neurological, and psychiatric disorders.
2. Develop tools and biomarkers to assess sleep sufficiency, sleep quality and circadian function, including molecular, cellular, and physiological signals in accessible tissues.
3. Identify the genetic variants that predispose to variations of sleep/circadian rhythms and sleep-wake disorders, as well as vulnerability to the effects of sleep loss and circadian dysfunction on behavior, cognition, and health.
4. Investigate the differential vulnerability to the effects of sleep deficiency with respect to clinical and societal factors such as life stage, chronic illness, health disparities due to social, demographic, environmental, and geographic attributes, and health inequalities secondary to racial, ethnic, socioeconomic, or educational attributes. These factors may influence the occurrence or consequences of sleep deficiency for the individual or the community.
5. Establish normative age- and gender-specific data for sleep duration, sleep quality, and circadian timing using both self-reported and objective sleep and circadian phenotyping in studies that include analysis of diverse ethnic and socioeconomic groups.
6. Design and evaluate intervention strategies assessing the impact of improved sleep and circadian alignment on physiological functioning, behavior, health, and well-being.

HARNESSING CLINICAL TRIALS, COMPARATIVE EFFECTIVENESS AND PERSONALIZED MEDICINE APPROACHES TO IMPROVE THE TREATMENT OF SLEEP AND CIRCADIAN DISORDERS AND REDUCE HEALTH DISPARITIES

Background

The health burden caused by chronic sleep deficiency described above indicates the high potential for effective sleep interventions to reduce morbidity, mortality, and health care costs, and to improve quality of life and public safety. There are numerous pharmacological and behavioral interventions and devices available for treatment of highly prevalent and morbid sleep disorders. Meta-analyses, including uncontrolled studies and/or some early randomized studies support use of: (a) CPAP for improving sleepiness, quality of life, and blood pressure in adults with sleep apnea [28-31]; (b) adenotonsillectomy for improving behavior and quality of life in children with sleep apnea[32]; (c) select hypnotics and cognitive behavioral therapy for improving sleep, perceived daytime function, and quality of life in chronic insomnia[33,34]; (d) drugs for treatment of excessive sleepiness in narcolepsy[35] and for cataplexy[36]; (e) dopamine agonists for reducing the frequency of leg movements, RLS symptoms, and improving sleep quality in RLS; (f) wake promoting agents and chronobiotic interventions to improve shift work disorder.[37]

There is a need to harness the power of alternative study designs and infrastructure resources to improve the prevention and treatment of sleep and circadian disorders. Development of cost-effective, patient-centered treatments for sleep disorders represents an opportunity to improve the health and quality of life of Americans and people worldwide, particularly in disadvantaged or vulnerable populations.

Opportunities and Needs

Research on the interaction between sleep/circadian rhythm disorders and chronic medical conditions represent a critical opportunity for the field. Examples of an adverse interactive effects include, but are not limited to, cardiovascular/cerebrovascular disease,[38-40] obesity, diabetes,[41,42] cognitive, behavioral and affective disorders, chronic respiratory diseases, adverse pregnancy outcomes,[43] cancer, infectious and inflammatory diseases, traumatic brain and spinal cord injuries, and neurodegenerative diseases. The critical question is whether treatment of sleep deficiency/sleep disorders modifies the course/outcome of these conditions. A particular area of opportunity, given the large public health burden and the fact that techniques now exist to diagnose neurodegenerative disorders such as Alzheimer disease before clinical symptoms develop,[44,45] is to determine whether sleep deficiency/sleep disorders represent modifiable risk factors that can alter disease progression.[46,47] Another example includes the treatment of insomnia relative to chronic/recurrent depression.

Understanding how to most appropriately utilize sleep disorder treatments, and identifying the impact of treatment on well-defined health outcomes, have been limited by a paucity of well-powered, controlled clinical trials. Whereas studies that address cardiovascular endpoints include thousands of person-years of follow-up, most sleep disorders intervention studies have been small, of short duration, and uncontrolled. For example, for sleep apnea, since 2000, there have only been 39 registered clinical trials, all with small sample sizes (average n = 200 subjects) and most assessing intermediate measures, such as blood pressure for less than 1 year, rather than more severe clinical outcomes such as cardiovascular events and mortality.[48] Studies of interventions for treating insomnia, narcolepsy, RLS, and shift work disorder have generally been even of shorter term (6 weeks to 6 months). The number of controlled trials in pediatric patients with sleep disorders is virtually negligible.

Lack of outcomes data prevents the establishment of high level evidence-based guidelines for the effective treatment of sleep disorders, resulting in: variation in care, inappropriate utilization of limited health care resources; inconsistent messaging to patients and the public; and inappropriate treatment decisions. There is a need to generate data that are broadly generalizable, evaluate the benefits and harms of alternative treatment strategies and address the priorities of patients. Thus, there are knowledge gaps that need to be addressed using both traditional clinical trial methodologies as well as approaches that use comparative-effectiveness strategies, patient-centered outcomes, which address specific patient characteristics (i.e., personalized medicine).

There are self-report instruments that give some indication of the impact on aspects of well-being and function specific to sleep disorders.[49-52] There is however, a need to extend this tool set by establishing objective instruments, measures and indices of clinical effectiveness, quality of life and patient-oriented outcomes that are specific and sensitive to sleep interventions. Technological development to objectively measure sleep and

circadian function in the general population at home, school and work are needed for "personalizing" therapy for individual risk factors and physiology, to validate and to incorporate these objective tools systematically in clinical care and clinical trials. Tools are needed that can be used to assess sleep health both general in nature, but also specific to particular sleep disorders. Tools are needed that can assess sleep health as differentiated by age, sex, and other indicators of health disparities.

Clinical and comparative effectiveness research in sleep medicine could be strengthened by leveraging information routinely collected in clinical settings. Incorporating key exposure and outcome measures for sleep and circadian disorders into the electronic medical record would enhance assessment of the impact of sleep disorders and their treatment on patient-centered outcomes. Furthermore, improved integration and standardization of sleep diagnostic data into electronic medical records would accelerate comparative effectiveness research and facilitate developing population-based approaches to medical management that will be part of the new patient-centered medical home. Advancing outcomes research will require collaborations of the sleep medicine community with major developers of electronic medical records, health maintenance organizations and insurance companies to ensure appropriate coding and collection of relevant metrics from large numbers of patients managed in "real world" settings.

One area of new opportunity is the Patient-Centered Outcomes Research Institute (PCORI). PCORI is authorized by Congress to conduct research to provide information about the best available evidence to help patients and their health care providers make more informed decisions. PCORI's research is intended to give patients a better understanding of the prevention, treatment, and care options available, and the science that supports these options.[53] PCORI has established many areas for research that are condition neutral. They are: (1) Assessment of prevention, diagnosis, and treatment options; (2) Improving healthcare; (3) Communication and dissemination research; (4) Addressing disparities; (5) Accelerating patient-centered outcomes research and methodological research; and (6) Improving infrastructure for conducting research through clinical data and patient-powered research networks.

The importance of sleep to the well-being of patients and the disproportionate burden of sleep disorders in minority and populations at risk for health disparities makes the area of sleep and circadian medicine an excellent candidate for these priorities. Particular areas of opportunity include: (1) assessing different approaches to treatment of sleep and circadian disorders in community settings; (2) comparing the current fragmented care model for sleep disorders to an integrated model; and (3) assessing how to approach sleep and circadian disorders in different populations. We know, for example, very little about optimizing adherence to treatment of sleep-disordered breathing in African Americans.[54] As pointed out by the Association of Black Cardiologists, the consequences of sleep apnea in African Americans is also very understudied.[55] In sleep medicine, there is a need for comparative-effectiveness research aimed at reducing and eliminating health disparities and their adverse consequences.

The advent of Accountable Care Organizations and the need for preventative medicine to bend the healthcare "cost curve" presents opportunities to sleep and circadian researchers. Specifically, there are opportunities to study the cost-effectiveness of healthcare systems that engage in early identification, treatment and continued prevention of sleep and circadian disorders and their impact on patient outcomes.[56] Another emerging opportunity is that of P4 medicine (predictive, personalized, preventive and participatory). These strategies require a systems medicine approach and are highly dependent on –omic strategies (genomics, proteomics, metabolomics, etc). Personalized medicine and pharmacogenetics is now well developed in oncology[57,58] and in treatment of cardiovascular disease where genetic information is used to inform therapeutic decisions.[59] While in its infancy, these approaches are beginning to be applied to sleep and circadian disorders. There is a need to incorporate these principles and technologies into studies of sleep and circadian disorders, including identifying and curating appropriate cells and tissues for use in research. Future integration of -omics data with rich phenotypic information from databases containing sleep and circadian data would provide opportunities for identifying culprit physiological pathways and to develop predictive and personalized strategies for combating disease. Given the crucial role of sleep and circadian pathways in multiple physiological systems, this systems medicine approach could lead to marked advances in treating both sleep disorders as well as other chronic diseases. Using the above approaches to identify novel pathogenetic pathways will lead to the need for new basic science investigations to determine mechanisms.

Recommendations:

1. The AASM, SRS, and other professional societies and patient organizations should work collaboratively to develop consensus documents defining relevant patient-centered outcomes that can be incorporated into routine clinical practice and also in research studies to promote the integration of outcomes evaluations across a broad range of clinical and research settings, making such outcomes assessments "routine" and "required."
2. Partner with insurers and vendors of electronic medical records to integrate relevant information about outcomes of management of common sleep disorders into electronic medical records to facilitate the collection, retrieval, and analyses of such data, improving their clinical application and use in outcomes-based research in real world settings.
3. Investigate and reduce the impact of chronic disease, healthcare disparity, and inequality on sleep and circadian disorders.
4. Promote the development of personalized sleep/circadian medicine through the identification and validation of individualized approaches to the management of sleep and circadian disorders.
5. Support basic science research on biological mechanisms that hold promise for developing new ways of understanding sleep and circadian disorders and generating new approaches to their diagnosis and treatment.
6. Support research to determine whether sleep deficiency/sleep disorders can modify course of prevalent chronic medical and neurodegenerative conditions and represent modifiable risk factors that can alter disease progression.

ESTABLISH RESEARCH NETWORKS AND INFORMATICS INFRASTRUCTURE

Background

To improve the efficiencies of all of the above, there is a need to establish appropriate informatics resources and networks to support large-scale, coordinated, and multidisciplinary studies and data resources. Several areas identified in the NIH Sleep Disorders Research Plan would immediately benefit from a sleep and circadian research network, in particular the treatment and management of sleep disorders and the influence of sleep deficiencies on outcomes in other medical conditions. The field could reach the goal of having high-level evidence-based clinical guidelines for treatment of sleep disorders, and for improving outcomes in other diseases, such as cardiovascular diseases, if there were evidence-based sleep management guidelines. In order to develop these necessary guidelines, large, coordinated clinical trials are needed, and a Research Network would supply the necessary support for these projects.

Opportunities and Needs

The sleep and circadian research field has some existing resources that could be leveraged to develop a comprehensive, formal research network infrastructure. The largest is the Sleep Research Network (SRN), which currently includes sleep researchers representing 55 US Clinical and Translational Science Award (CTSA)-funded institutions. Other efforts at network development include the Academic Alliance for Sleep Research (AASR) funded by an industry foundation grant, and the International Collaboration of Sleep Apnea Cardiovascular Trialists (INCOSACT), that was established to promote global collaborative trials by sharing tools, data and expertise. However, none of these entities have the budgetary capacity to support data resources or to fund pilot or larger studies.

A comprehensive national sleep and circadian sleep research network would facilitate increased efficiency and cost effectiveness in the development, implementation and evaluation of studies of alternative interventions or health care delivery models, and the rapid dissemination of findings. Supporting collaborative trials and further engaging the broad scientific community in sleep and circadian research also would benefit from access to informatics platforms for organizing and harmonizing sleep and circadian-related data. The National Center for Research Resources and the Agency for Healthcare Research and Quality provide resources that have led to the community's development of web portals and other informatics tools, including clinical trial management tools and query tools that allow data across studies to be identified and aggregated; these can be further leveraged from a national to a global resource.

A major factor impeding progress in identifying specific biological mechanisms for sleep and circadian disorders and for translating findings to clinical practice is the lack of access to large, well-annotated databases. Addressing critical questions in a statistically robust way is best accomplished by analysis of specimens and data from samples that exceed the scope of studies from single centers. There is a need to develop a culture and infrastructure that supports the collection, aggregation, and dissemination of large, complex, and well-annotated datasets containing the full spectrum of clinical, physiological, imaging, genetic, and other data relevant to sleep medicine and its many related health areas. As observed by Dr. Francis Collins, Director of the NIH: "The era of 'Big Data' has arrived. There is an urgent need and opportunity for increased collaboration and coordination of access to, and analysis of, the many different data types that make up this revolution in biological information, including genomics, imaging and phenotypic data from electronic health records."[60,61]

Further development of data resources could greatly enhance the discovery of genes and biological mechanisms for sleep and circadian disorders, thus, paving the way for personalized medicine. There is clear evidence for significant heritability for most sleep and circadian disorders. Data from initial genome wide association studies and candidate genes studies also implicate circadian genes in the pathogenesis of metabolic and other chronic disorders. Gene variants have been identified that increase the risk of restless legs syndrome, as well as immune genes in the pathogenesis of narcolepsy. Research on the genetic mechanisms for sleep and circadian disorders, however, has been limited by lack of well-organized datasets containing genomic and well-annotated phenotype data on large samples. Systematic efforts at developing appropriate data sources are needed to elucidate specific biological pathways for sleep/circadian disorders that can be targeted for future interventions or to understand factors that modify disease susceptibility. Large data sets are especially needed to test gene by environmental interactions.

A formal sleep and circadian research network is needed to facilitate the conduct of large-scale, coordinated, and multidisciplinary studies and to develop robust data platforms needed to address multiple gaps in clinical medicine and biological science. Further investment in centralized data resources, data query tools, and data repositories are also needed to enhance access to and development of genetic, physiological, neuroscience, behavioral, and clinical data and to create new data resources to prospectively address sleep-related health outcomes and to collect relevant biomarkers.

Given the essential role that a sleep/circadian research network would play, the SRS, AASM, and government stakeholding agencies should work in partnership to create and maintain an infrastructure to ensure that it serves the larger field of sleep and circadian researchers and contributes to progress in the field toward greater support for sleep and circadian health. Professional medical and research associations should play a key role in collaborating with relevant program staff at NIH, at PCORI, and with patient groups in organizing and supporting this effort.

Recommendations:

1. Support the development of sleep research networks and disease registries including informatics, clinical trial infrastructure, core laboratory, and research network resources.
2. Promote the utilization of open source data and tools resources across sites to maximize data sharing and standardization.
3. Promote the utilization of open source data and tools resources across sites to maximize data sharing and standardization.

4. Establish appropriate governance of networks so that they are responsive to the needs of the field of sleep and circadian research broadly, and that they are sustainable.

ENHANCE SLEEP AND CIRCADIAN RESEARCH TRAINING

Background

Goal five of the 2011 NSCDR Strategic Research Plan is to "enable sleep and circadian research training to inform science in cross-cutting domains, accelerate the pace of discovery, and the translation of enhanced therapies from bench to bedside to community." An analysis of the state of the field reveals the following trends in current training awards in sleep and circadian science. In March 2013, there were 38 sleep or circadian focused F32 postdoctoral awardees at 30 institutions supported by 12 Institutes at NIH (~60% split evenly between NIMH, NIDDK, NEI, NIGMS, and 40% in NHLBI). Regarding K mechanisms, the sleep and circadian field has 57 K23s at 12 Institutes (30% of which are under NHLBI) and 11 K08s in 6 Institutes (4 in NHLBI). K99 grants with sleep or circadian keywords were found at 6 ICs, for a total of 10 awards (1 in NHLBI).

Research in genomics and epigenetics of sleep and circadian factors is mentioned throughout the 2011 National Sleep Disorders Advisory Plan, yet there are only 10-K awards at the trainee level addressing genetics/genomics and none focused on epigenetics. Patient-centered outcomes are also a crucial component of the 2011 Plan and increasingly important in medicine in the era of the Affordable Care Act, yet no sleep K awards address this important field. *To put it in perspective, given that 50-70 million Americans suffer from sleep disorders, our field is training less than one clinical sleep and circadian investigator per annum per 1 million patients.*

There are 7 institutionally based T32 training programs in sleep and circadian research housed at 6 institutions. By comparison, the Lung Division of the NHLBI, in which the National Center on Sleep Disorders Research (NCSDR) is housed, has 39 T32 grants for lung disease. Taken together, it appears that the future of sleep and circadian research may lack the knowledge, expertise, and workforce numbers to address the important questions needed to improve our understanding of sleep and circadian health, improve patient outcomes, and move the field forward.

The American Academy of Sleep Medicine (AASM) and Sleep Research Society (SRS) and their respective foundations (American Sleep Medicine Foundation [ASMF] and Sleep Research Society Foundation [SRSF]) have worked for years to prepare and engage sleep researchers of the future. Annual trainee days in conjunction with the Associated Professional Sleep Societies meeting, an annual trainee workshop at the National Institutes of Health, early career starter grants, and bridge to K award grants are but a few of the many ways these entities are working to create a robust sleep research workforce moving forward. Nonetheless, the Joint Task Force acknowledges the need for still greater efforts to revitalize the sleep research trainee pipeline.

Opportunities and Needs

T32 training grants, although effective at launching research careers, can be difficult to obtain due to requirements for a large and broad-based sleep research group to mentor young investigators. Sleep medicine is still a relatively young field, and many programs lack the critical mass to support a successful T32 application. A creative solution to this conundrum is to pool resources across academic institutions to foster successful applications. Web-based and other educational technologies make remote mentoring possible. The recent success of a multi-institutional T32 on genetic and genomic approaches to sleep disorders funded by the NHLBI represents a paradigm shift and one that could be adopted in other needed areas for sleep and circadian research. Increasing sleep and circadian education in medical school curricula has been a long term goal of the AASM and SRS. However, the Medical School curriculum is very tightly packed and difficult to alter. One creative proposal involves utilizing an R25 education grant mechanism to create a sleep educational module for 3rd and 4th year medical students in their clinical case rotations. Ultimately, the hope is that earlier exposure to sleep and circadian research may provide the spark for trainees and early stage investigators to consider a sleep and circadian research career.

Other opportunities to increase the sleep research workforce involve a "cross-pollination" strategy that promotes collaboration as Co-PI's with researchers from other complementary fields on training and career development initiatives. Other mechanisms may be explored, within individual Institutes of the Trans-NIH Sleep Research Network, to provide additional training to our current sleep research workforce to diversify their skill set in areas of importance as highlighted in the 2011 Sleep Disorders Research Plan. Large, readily available datasets that include sleep measures may attract epidemiologists or geneticists or other basic research scientists to the sleep and circadian field with hopes they may continue this line of investigation throughout their careers.

At present, the NHLBI is the sole NIH Institute fostering T32 for sleep research training. The Trans-NIH Committee on sleep research provides an opportunity to broaden this support to other Institutes with a stake in the 2011 Plan. Sleep and Circadian Medicine by its very nature is cross-disciplinary, and there is a vested interest in training the next generation of sleep and circadian researchers that is cross-institutional.

In conclusion, the 2011 NSCDR Strategic Research Plan sets a compelling agenda for the future of sleep medicine research. With technological growth in research methodologies, there has never been a more exciting time to pursue sleep and circadian scientific investigation. The current pipeline of trainees is not full, but implementation of the creative approaches addressed above will help catalyze enthusiasm for sleep and circadian research and ensure the next generation of sleep and circadian researchers.

Recommendations:

1. The sleep and circadian research community should seek to expand T32 grants in basic and translational science to Institutes beyond the NHLBI and explore adding slots to existing T32s in areas such as genomics, systems biology, translational/patient-oriented research and patient-centered outcomes research.
2. The sleep and circadian research community should explore developing additional T32 multi-institutional

training grants in areas relevant to the Strategic Plan for sleep and circadian research.

3. The sleep and circadian research community should develop academic electives and resources focused on sleep and circadian health and sleep and circadian physiology for use by professional programs including medical schools (allopathic and osteopathic), clinical psychology, graduate nursing programs, dental schools, and physician assistant schools.
4. The sleep and circadian research community should seek to attract talented researchers in other fields to address important sleep related research questions through engagement as collaborators on proposals and encourage the development of sleep focused interdisciplinary basic and translational science training funding opportunities.

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