RESTLESS LEGS SYNDROME FOUNDATION

Restless Legs Syndrome Foundation
Legislative Agenda
116th Congress, 1st Session

About The Foundation

The Restless Legs Syndrome (RLS) Foundation is a 501(c)(3) nonprofit organization dedicated to improving the lives of men, women and children who live with restless legs syndrome (RLS), an often devastating disease. Founded in 1989, the Foundation's goals are to increase awareness, improve treatments and, through research, find a cure for RLS. The Foundation serves healthcare providers, researchers, 5500 members, and millions in the United States and around the world who have RLS. The RLS Foundation has members in every state, local support groups, and a research grant program that has awarded over $1.8 million to fund medical research on RLS causes and treatments.

About Restless Legs Syndrome

RLS is a serious neurological disease that devastates the lives of millions of Americans. An estimated 12 million men, women and children in the US have RLS. One in 33 adults (3 percent) needs daily clinical treatment. Treatment is life-long, and there is no cure for RLS. People with RLS experience an overwhelming, agitating and uncontrollable urge to move their legs, which can only be relieved by moving or walking to abate the sensation. RLS is at its strongest in the evening and night time hours, severely disrupting sleep. It is 3-4 times more common in women than men and is twice as common in older Americans.

The sleep loss caused by RLS robs people of the ability to work and live normally and may lead to depression, anxiety and suicidal thoughts. The RLS Foundation loses members every year to suicide because their symptoms become unbearable. Profound sleep loss puts people with RLS at risk for hypertension, diabetes, heart attack, stroke and Alzheimer's disease.

RLS treatment options are limited; FDA-approved RLS treatments do not provide life-long coverage. First-line medications don't work for some patients, and over time actually make the disease worse for many others due to a serious side effect of therapy known as augmentation. For the millions of people who have chronic, unrelenting, nightly RLS symptoms, opioids are an established, highly effective treatment option when first-line therapies have failed. Opioids bring dramatic relief to an estimated 90–95 percent of RLS patients.

However, RLS is not chronic pain; RLS has a distinctly different underlying neuropathology. Clinical experience among experts who use opioids to treat severe RLS has not shown the degree of drug misuse, dependency or addiction that is commonly associated with opioid use to treat chronic pain. RLS is a neurological disease impacting sleep and is best managed by neurologists and sleep specialists. RLS expert experience indicates that the dose of opioids used to manage RLS is significantly lower than used to treat chronic pain effectively. Guidelines published in Mayo Clinic Proceedings are available for clinicians to appropriately prescribe opioids for RLS.

From the Patient's Perspective

"I have suffered with RLS for almost 15 years following a total knee replacement. I used to be on Requip, but following my augmentation, this medication only makes my symptoms worse. For 5 years, I have been fortunate to be on a very effective treatment regimen that includes a low dose of Oxycontin at bedtime. In the last year, I moved to Florida and have yet to find a physician willing to continue this treatment, despite my efforts to educate them by sharing clinical guidelines on safe and proper prescribing of opioids for RLS. I am worried that I may lose the ability to treat my disease and suffer needlessly, because state and federal policies are being misapplied to prevent the appropriate use of opioids to treat RLS."

-Sandy Katanick, RLS Foundation Board of Directors

Legislative and Policy Priorities

Medical Research

- **Please provide the National Institutes of Health (NIH) with at least $41.6 billion in fiscal year (FY) 2020, a $2.5 billion funding increase.** Important research on RLS is funded across NIH Institutes and Centers, including the National Institute of Neurological Disorders and Stroke (NINDS), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH). Sustained funding commitments are needed to identify better treatments and a cure for this devastating disorder.

- **Please continue to include "sleep disorders" in the Department of Defense Peer-Reviewed Medical Research Program (PRMRP) for FY 2020.** RLS is a major sleep disorder that affects an estimated 40,000 active duty military personnel and readiness.

Patient Access to Appropriate Treatments

- **Please accommodate the needs of patients who rely on the regular use of low-total daily doses of opioids to manage their RLS.** As you consider new legislation and work with federal agencies to address the opioid epidemic, please support a diagnosis-appropriate *safe harbor* for RLS patients, so they do not face arbitrary barriers. RLS patients need for their physicians to be able to prescribe opioids appropriately and without undue restriction.

Education and Awareness

- **Please provide $5 million for the National Neurological Conditions Surveillance System (NNCSS) for FY 2020.** The NNCSS at the Centers for Chronic Disease Control and Prevention (CDC) collects and synthesizes data to help increase our understanding of neurological disorders and to support further neurologic research. RLS remains a severely misunderstood and underdiagnosed neurological disorder, and increased surveillance is vital to improving patient outcomes.

- **Please provide at least $250,000 in line-item funding for sleep and sleep disorders public health activities at the CDC's Center for Chronic Disease Prevention and Health Promotion.** With the cessation of the National Healthy Sleep Awareness Project (NHSAP), CDC presently has no active public health activities dedicated to sleep or sleep disorders, despite the fact that sleep affects nearly every body system and many chronic diseases. Please allow the valuable scientific and public health efforts started during the NHSAP to continue.

RESTLESS LEGS SYNDROME FOUNDATION

Restless Legs Syndrome Foundation
The Opioid Crisis and Patient Access to Effective Therapy
Statement of Principles

About The Foundation

The Restless Legs Syndrome (RLS) Foundation is a 501(c)(3) nonprofit organization dedicated to improving the lives of men, women and children who live with restless legs syndrome (RLS). Founded in 1989, the Foundation serves healthcare providers, researchers, 5500 members, and millions in the United States and around the world who have RLS. The RLS Foundation has members in every state, local support groups, and a research grant program that has awarded over $1.8 million to fund medical research on RLS causes and treatments.

Restless Legs Syndrome and Opioid-Based Therapy

Restless legs syndrome (RLS) causes unpleasant or uncomfortable sensations in the legs together with an uncontrollable urge to move them. The National Institute of Neurological Disorders and Stroke (NINDS) describes RLS as a neurological sensory-motor disorder whose symptoms are produced within the brain. It is estimated that up to 5 to 7.5 percent of Americans may have RLS.

There is currently no cure for this disease and any symptomatic relief achieved with medications is not guaranteed to work forever. Therefore, all potential treatment options that are known to be effective treatments for RLS, need to be available to the individual.

Opioid medications in low-total daily doses are a recognized, effective treatment for managing RLS when alternative first-line medications do not work or become ineffective. Clinical studies and the experience of RLS-experts indicate that the average total-daily dose of opioids used to manage RLS is significantly lower than doses prescribed to treat chronic pain. Research has also demonstrated that utilization of these therapies to manage RLS does not show clinical indications of addiction or drug tolerance.

Due to the devastating nature of RLS, if patients were to lose access to these therapies, they would also lose the ability to effectively manage their disease.

Key Issues for Policymakers:

- RLS is a neurologically-based sleep disorder, and therefore, management should not fall under the exclusive purview of pain-management specialists when opioids are indicated. The underlying neuropathology in RLS is quite different from that associated with chronic pain. Therefore, long-term outcomes for opioid use in RLS should not be extrapolated from their use in chronic pain.
- The total daily dose of opiates commonly used to treat RLS is often lower than that used in managing chronic pain, which dramatically reduces the risk of tolerance and dependency.
- RLS patients and their physicians need assurance that regulations designed to curb abuse of opiates do not inadvertently penalize patients suffering from a serious disease who have exhausted other treatments. Regulations that seek to limit refills, require frequent doctors' visits and co-payments, or erect other barriers can have a devastating effect on RLS patients with no countervailing public health or safety benefit.
- Any legislation, policy, or regulation must account for the specific needs of RLS patients and not paint them with the same broad brush as other communities utilizing (and often struggling with) opioid-based treatments.

RLS Foundation Research Grant Program: 1997–2018

The RLS Foundation Research Grant Program supports basic and clinical research on restless legs syndrome (RLS).

In 1997, the RLS Foundation established the Research Grant Program to fund small research grants ($25,000–$35,000) to stimulate and provide data for larger grants at federal agencies such as the National Institutes of Health, Department of Defense, biotechnology and medical technology companies. Funding priorities include basic and clinical research to promote a better understanding of the disease, advance new treatments and find a cure for RLS. The Research Grant Program invites innovative approaches, interdisciplinary studies and support of promising postdoctoral candidates.

The primary areas of funding have been genetics, epidemiology, iron regulation, neurophysiology and animal models/treatment. The Foundation's Scientific and Medical Advisory Board reviews grant applications and selects studies for funding based on scientific merit and alignment with funding priorities.

Since the grant program began, the Foundation has funded 44 research grants totaling nearly $1.8 million. Eighty-three percent of the grant recipients reside in the United States and the remaining seventeen percent of grant recipients are international. The average grant amount is $39,927.

Ten of the recipients secured additional funding for their studies from government agencies, for total grant award dollars of over $10 million. Recipients have published findings in over 22 papers and several book chapters.

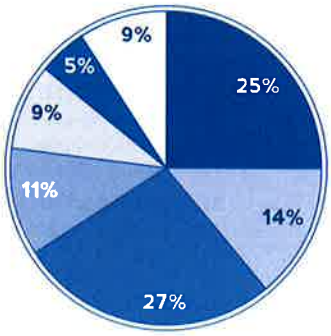
Research study uncovers gene variant for RLS

In 2007, Dr. David Rye, funded in part by the RLS Foundation, discovered the first gene variant that contributes substantially to the risk for RLS. More recently, in 2017 Dr. Sergi Ferré, with research grants from the RLS Foundation, has hypothesized that the reason for increased glutamate and dopamine transmission in RLS is due to a decrease in adenosine (which exerts a brake on both systems) transmission. It has been known for some time that the increased dopamine and glutamate transmission leads to PLMS and hyperarousal in RLS. The researchers have also pinpointed a subtype of receptor in the brain – the dopamine D4 receptor –as a new and better target for dopamine drug development.

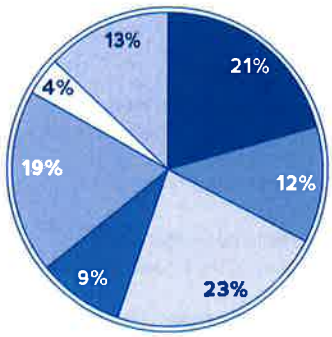
This influential research significantly advanced understanding of the causes of the disease, paving the way for future improvements in diagnostic methods and treatments.

To keep this great work moving forward toward a cure, please contribute to the RLS Foundation Research Grant Program at www.rls.org or call 512-366-9109.

% Studies



% Funds



Grants by Priority Area, 1997–2018

Priority Area	Number	Percent of Studies	Award	Percent of Funds
Genetics	11	25%	$368,954	21%
Iron Regulation	6	14%	$206,311	12%
Animal/Treatment Models	12	27%	$397,299	23%
Neurophysiology	5	11%	$157,500	9%
Epidemiology	4	9%	$326,356	19%
Dopamine	2	5%	$69,600	4%
Miscellaneous	4	9%	$230,782	13%
TOTAL	42	100%	$1,756,802	100%

Grant Award Recipients

Genetics

Lan Xiong, MD, PhD (2009)
Genome wide gene expression profile & iron regulation in RLS patients carrying the MEIS1 genetic risk variant
McGill University, Montreal, Canada

Guy Rouleau, MD, PhD (2008)
Defining the risk variants within the MEIS1, BTBD9, MAP2K5/LBXCOR1 genomic regions in RLS patients
Human Research Centre, Notre Dame Hospital, Montreal, Canada

Juliane Winkelmann, MD (2008)
Worldwide genome-wide association study for RLS: WW-GWA-RLS
Institute of Human Genetics
GSF National Research Center, Munich, Germany

David B. Rye, MD, PhD (2006, 2007, 2008)
RLS genome study - USA/ICELAND
Emory University School of Medicine, Atlanta, GA

Juliane Winkelmann, MD (2005)
EU-RLS-GENE – Three loci for RLS on chromosome 12q (RLS-1); 14q (RLS-2); and 9p (RLS-3) mapping study
Institute of Human Genetics
GSF National Research Center, Munich, Germany

Lan Xiong (2003)
Dissecting Genes Involved in Restless Legs Syndrome in French-Canadian Population with Elevated Prevalence
McGill University, Montreal, Canada

David B. Rye, MD, PhD (2002, 2004)
Genetic linkage analysis of RLS in Iceland
Emory University School of Medicine, Atlanta, GA

Guy Rouleau, MD, PhD (1999)
Searching for genes predisposing to restless leg syndrome in the French-Canadian population
Montreal General Hospital Research Institute, Montreal, Canada

Iron Regulation

Padmavathi Ponnuru, PhD (2011)
A role for MEIS1 in brain iron deficiency in Restless Legs Syndrome
Drexel University College of Medicine, Philadelphia, PA

Stephanie Miller Patton, PhD (2006)
The contributory role that iron-sulfur cluster proteins play in RLS
Pennsylvania State University College of Medicine, Hershey, PA

Stephanie Miller Patton, PhD (2005)
The contribution of iron regulatory proteins (IRPs) to the dysregulation of iron homeostasis in RLS
Pennsylvania State University Milton S. Hershey Medical Center, Hershey, PA

James R Connor, PhD (2003)
Is Defective Transferrin Receptor Expression in the brain the underlying cause of RLS?
Pennsylvania State University Milton S. Hershey Medical Center, Hershey, PA

James R. Connor, PhD (2001)
Elucidating mechanisms for regulation of iron acquisition by the brain
Pennsylvania State University, University Park, PA

Judith Owens, MD, MPH (1999–2000)
Restless leg and periodic limb movements in children with iron deficiency anemia and elevated lead
Brown University School of Medicine, Providence, RI

Animal/Treatment Models

Sergi Ferré, MD, PhD (2014, 2015)
Measuring corticostriatal neurotransmission in iron-deficient rats as a model for screening of drugs potentially useful in WED-RLS.
National Institute on Drug Abuse, Baltimore, MD

Yuqing Li, PhD (2015)
Characterization of Meis1 heterozygous knockout mice as a model of Willis-Ekbom Disease
University of Florida, Gainesville, FL

Yuan-Yang Lai, PhD (2012)
Effect of histamine H3 receptor antagonism on PLM in iron-deficient rats: an animal model of RLS and its treatment
University of California Los Angeles and Sepulveda Research Corporation, Los Angeles, CA

Subhabrata Sanyal, PhD (2011)
Genetic modeling of Restless Legs Syndrome in Drosophila
Emory University School of Medicine, Atlanta, GA

Seiji Nishino MD, PhD (2004)
PLMS in hypocretin-deficient narcoleptic dogs
Stanford Center for Narcolepsy Research, Palo Alto, CA

Byron C. Jones, PhD (2004)
Proposal to create mouse colony to identify candidate genes related to RLS
Pennsylvania State University, University Park, PA

Yuan-Yang Lai, PhD (2002)
Ventral mesopontine junction mediated muscle activity during sleep
University of California, Los Angeles, North Hills, CA

Felipe Espinosa, DVM, PhD (2001–2002)
Potential mouse model for human-RLS (hRLS)
University of Texas Southwestern Medical Center, Dallas, TX

David B. Rye, MD, PhD (2001)
Neural substrates of and pharmacologic interventions for restless legs syndrome and paroxysmal limb movements during sleep
Emory University School of Medicine, Atlanta, GA

David B. Rye, MD, PhD (2000)
Fellowship for Drs. Amanda Freeman and Glenda Keating - Non-human primate model of PLMS
Emory University School of Medicine, Atlanta, GA

Michael Polydefkis, MD (2000)
A Trial of gabapentin in RLS stratifying patients by presence/absence of small fiber neuropathy
Johns Hopkins University School of Medicine, Baltimore, MD

Neurophysiology

Stephanie Miller Patton, PhD (2012)
The role that the nitric oxide pathway plays in regulating vasodilation of the legs in Restless Legs Syndrome
Pennsylvania State University College of Medicine, Hershey, PA

Stephanie Miller Patton, PhD (2009)
The role that the hypoxia response pathway & neuronal nitric oxide synthase (nNOS) plays in the mechanism of RLS
Pennsylvania State University College of Medicine, Hershey, PA

Douglas E. Wright, PhD (2006)
Contributions of Abnormal Sensory Input from Muscle in RLS
University of Kansas Medical Center, Kansas City, KS

Karin Stiasny-Kolster, MD (2004)
Quantitative sensory testing (QST) in RLS
Department of Neurology, Marburg, Germany

William Bara-Jimenez, MD (1997–1999)
Fellowship
National Institute of Neurological Disorders and Stroke, Bethesda, MD

Epidemiology

Hochang Benjamin Lee, MD (2013)
Subcortical white matter hyperintensities on brain magnetic resonance imaging: a comparison between early-onset and late-onset RLS subjects
Yale University, New Haven, CT

Jeffrey Durmer, MD, PhD (2005)
Identification of restless legs syndrome in children
Emory University School of Medicine, Atlanta, GA

Lorene M. Nelson, PhD and Stephen V. Van Den Eeden, PhD (2004)
Pilot study of restless legs syndrome in Kaiser Permanente
Stanford University School of Medicine, Stanford, CA
Kaiser Permanente Division of Research, Oakland, CA

Christopher J. Earley, MD, PhD (2001)
Epidemiological study of an elderly twin cohort
Johns Hopkins University Bayview Medical Center, Baltimore, MD

Dopamine

Shawn Hochman, PhD (2003)
Spinal Dopamine Dysfunction and Restless Legs Syndrome
Emory University School of Medicine, Atlanta, GA

David Eidelberg, MD (2002)
A quantitative whole-brain imaging study of the dopamine transporter in the RLS using FP-betaCIT PET Scanning
North Shore University Hospital, Manhasset, NY

Miscellaneous

John Winkelman, MD, PhD (2017)
Multicenter Longitudinal Pilot Observational Study of Efficacy and Tolerability of Long-term Treatment of Restless Legs Syndrome Using Opioids
Harvard Medical School/Massachusetts General Hospital, Boston, MA

William Ondo, MD (2016)
Treatment of RLS augmentation with Ecopipam, A D1 Specific Antagonist
Houston Methodist Neurological Institute, Houston, TX

William Padula, PhD, MS, Msc (2016)
Economic Evaluation of Restless Legs Syndrome (RLS)
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

William G. Ondo, MD (2000)
Assistance with the Harvard Brain Tissue Resource Center
Baylor College of Medicine, Houston, TX

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RESTLESS LEGS SYNDROME FOUNDATION

The RLS Foundation is dedicated to improving the lives of the men, women and children who live with this often devastating disease. Our mission is to increase awareness, improve treatments and through research, find a cure for restless legs syndrome.

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THE SLEEP SPECIALISTS

Should Opioids Be Prescribed for Restless Legs Syndrome?

RLS expert John Winkelman, MD, PhD, has undertaken the long-term research needed to find out

Nasal Pillow Interfaces
Trends in the mask category

OTC Sleep Aids
What your insomnia patients need to know

Oral Appliance Reimbursement
An update on Medicare coverage

John Winkelman, MD, PhD, sees patients with restless legs syndrome at Massachusetts General Hospital. He is also a professor of psychiatry at Harvard Medical School and has done extensive research on the mechanisms behind RLS.

Should Sleep Specialists Prescribe Opioids for Restless Legs Syndrome?

John Winkelman, MD, PhD, was fooled once by an RLS therapy. Now he's launched a registry to do the long-term research that won't let the sleep medicine community be fooled twice.

By Lisa Spear

Photography by Jeffrey Andree/Massachusetts General Hospital Photography

As a clinician scientist, John Winkelman's research projects have almost always been driven by the perplexing cases he sees in clinic at Massachusetts General Hospital, particularly by patients who live with the neurological sleep disorder restless legs syndrome (RLS).

A professor of psychiatry at Harvard Medical School and a leader in the study of the mechanisms behind the condition, Winkelman, MD, PhD, has made enormous contributions to the medical field over the last few decades. He's investigated treatment options for patients with kidney failure and RLS. He observed how limb movements during sleep can increase heart rate and blood pressure, which could have cardiovascular implications for people with RLS. Now, in light of studies linking RLS augmentation with dopamine agonist therapy, he is looking at opioid therapies.

Despite published clinical trials showing the efficacy of opioids in treating severe RLS, the national opioid epidemic has made many clinicians wary of prescribing these medications, and patients often report difficulty obtaining opioid prescriptions for RLS, according to a guideline paper published in *Mayo Clinic Proceedings* in January 2018.[1]

"A lot of doctors are abrogating their responsibility because they are scared," says Winkelman, coauthor of the guidelines.

"I understand that because I am also nervous about prescribing these medications, but I want to do everything that I can to make sure that my patients' RLS is safely and effectively managed."

David Rye, MD, PhD, a neurologist based in Georgia who treats RLS, has found that some of his patients can benefit from opioids, but writing prescriptions for these medications comes with red tape. Many pharmacies don't take prescriptions from out of state—and since many people come from far away to see him, prescribing becomes a challenge, he says.

"Some physicians have just decided that they are not going to prescribe [opioids]. Several people in my office refuse to prescribe the medications. It's not only a burden to the patients, it's a burden to me because I end up seeing these patients," he says.

Should sleep medicine doctors prescribe opioids for RLS? It's a question that Winkelman is organizing a clinical workshop around at the annual SLEEP meeting in June in San Antonio, Texas. There, he hopes that prominent researchers, physicians, and regulators will debate the issue, share ideas, and potentially bridge gaps in understanding.

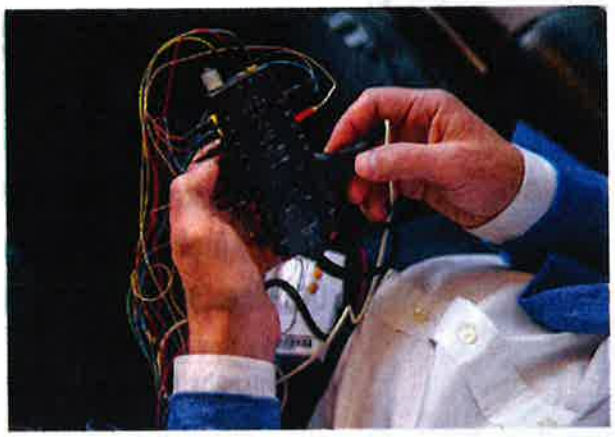
The question of RLS and opioids is one that he has already been exploring with funding from the Restless Legs Syndrome Foundation, which in 2017 awarded him a grant for a pilot study. With that funding, he has been building a registry of people in the United States who are prescribed opioids for RLS (registry information is available at www.massgeneral.org/rls-registry). In February, the RLS Foundation announced it is giving Winkelman an additional grant to extend his work in this area.

"This is the first study in which patients with RLS who use opioids are monitored over time to evaluate the effectiveness and tolerability of this treatment long-term, and by far the largest observational study of such patients," says Karla Dzienkowski, executive director of the foundation, in a statement.

Evaluating this therapy has become more important than ever since dopamine agonists, drugs that had long been considered the gold standard of treatment, are no longer a viable option for many patients. In recent years, it's come to light that as many as 50% to 70% of patients using these medications develop a severe worsening of symptoms called augmentation within 10 years.[2,3]

STORY CONTINUES ON PAGE 16

Winkelman's office at Massachusetts General Hospital provides a view of the West End neighborhood of Boston.



Winkelman sets up a sleep study device.

In such cases, RLS symptoms spread to the upper extremities and start earlier and earlier in the day.

Winkelman contributed to some of the first clinical trials showing the efficacy of two medications that were approved by the FDA in the United States for the treatment of RLS in the 2000s: pramipexole and ropinirole, which are dopamine agonists sold under the brand names Mirapex and Requip.

At first, these medications seemed like miracle drugs. "They, at least in the short-term, are incredibly effective for RLS, just like putting a piece of butter on a hot pan. The RLS really melts away in almost everybody," he says.

The clinical trials for FDA approval were only 3 months long but years later it became apparent in longer treatment that, unfortunately, in many people RLS becomes worse over time on these medications. "It became clear as I was treating these people that we had made a mistake," says Winkelman. "I began seeing more patients who were on high-dose dopamine agonists and had this very clear and very severe augmentation. So it became a challenge as to how to treat those people."

Physicians who don't recognize the phenomenon of augmentation continue to increase the dopamine agonist doses for patients whose symptoms worsen, unknowingly causing potentially permanent damage. "My experience is that some degree of augmentation is reversible, but for many people it is not," Winkelman says, "so you need to treat what is now the more severe aspects of restless legs syndrome."

Winkelman joined an international task force, established by the International Restless Legs Syndrome Study Group in conjunction with the European Restless Legs Syndrome Study Group and the RLS Foundation, to develop evidence-based recommendations for the prevention and treatment of dopaminergic-induced augmentation. In 2016 the group published a paper in the journal *Sleep Medicine*, stating that in the most severe RLS augmentations cases, when all else fails, methadone or oxycodone should be considered.

The RLS Registry will remain open to new participants until late June 2019. Enrollment is limited to individuals who have a diagnosis of RLS, are taking an opioid medication to treat their RLS symptoms, and have previously taken or are currently taking a dopamine agonist for RLS treatment. For information about participating, visit www.massgeneral.org/rls-registry or call 617-643-2082.

Continue this discussion in person at SLEEP 2019. Winkelman is organizing a clinical workshop, entitled "Should Sleep Medicine Providers Prescribe Opioids for RLS?" It will take place Tuesday, June 11, 2019, from 8 am to 10 am (room number to be decided; check the program closer to the date).

gabapentin and pregabalin. The third class is [intravenous] iron or oral iron in people who have lowish serum iron, and the fourth is opioids. So we don't have unlimited options," says Winkelman.

To bring awareness to this issue, Winkelman has visited Washington, DC several times over the last 6 months to talk to regulators from agencies including the US Department of Health and Human Services and the US Food and Drug Administration.

During these trips, he's asked the question: "How can we continue to address the significant opioid problem we have in this country, but at the same time recognize that doctors need to know that there are legitimate uses of opioids, such as RLS?"

Low doses of opioids can offer some relief, but Winkelman wants to proceed with caution. More data is needed about the long-term effects of opioids on RLS patients. This is why he devel-

"There are only four really well-established treatment categories for RLS. One are the dopamine agonists; the second, alpha-2-delta agents;

oped the National RLS Opioid Registry, based at Massachusetts General Hospital in Boston. The project has grown larger than expected, enrolling roughly 400 participants in the last year, far

In November, Winkelman traveled with representatives from the Restless Legs Syndrome Foundation to Washington, DC, to visit legislators and federal agencies involved in health care policy. Left to right: Lina Kilani, legislative correspondent, Sen. Lamar Alexander's office, Winkelman, Karla Dzienkowski, executive director of the RLS Foundation, Sandra Katanick, member of the RLS Foundation Board of Directors. *Photo courtesy of the RLS Foundation.*

Winkelman has been building a registry of people in the United States who are prescribed opioids for RLS, after realizing that dopamine agonists are not a viable long-term treatment for many patients.

surpassing the original goal of just 200.

In his clinical practice, Winkelman uses the Opioid Risk Tool, a well-established rating scale to help clinicians determine patients' likelihood of misusing or abusing opiates. The form is available for free online (www.drugabuse.gov/sites/default/files/files/OpioidRiskTool.pdf) from the National Institutes of Health.[3]

Winkelman typically prescribes methadone for RLS, a synthetic opioid that is known to treat pain, without producing the same intoxication that natural opiates are known for. According to the *Mayo Clinic Proceedings* paper, opioid medications most commonly used for RLS are oxycodone and methadone, but tramadol, codeine, morphine, and hydrocodone can also be considered. Effective doses are considerably lower than those used for chronic pain, 10-30 mg daily for oxycodone or 5-20 mg for methadone.[1]

According to Winkelman, researchers still have more to learn. The National RLS Opioid Registry already has 6 to 12 months of data for about half of those who have enrolled and retention rates have exceeded expectations.

The team has identified physicians who are willing to provide brochures about the registry to their patients. Those who are interested in participating can contact the researchers at Massachusetts General. The registry is enrolling new participants until late June 2019.

"We are going to continue to follow the participants for at least 5 years and hopefully longer," says Winkelman. "We really need long-term safety and efficacy data to provide to patients, to doctors, and to regulators."

Participants are given an initial phone interview and an online

other approaches: iron, gabapentin, pregabalin," says Winkelman, "so [opioids] are really last-ditch treatments."

One previous double blind, randomized study in the journal *Lancet Neurology* found that prolonged release oxycodone-naloxone was effective for short-term treatment in patients with severe restless legs syndrome not controlled with other treatments.[6] "The study followed patients for a year, but that is not long enough," says Winkelman.

"I've been through this once with the dopamine agonists, doing what I thought was best for my patients, and what was expert standard of care. But it turned out not to have been a good thing," he says. "A lot of people did get tremendous relief from the dopamine agonists, but we did not anticipate that in the longer term it would make their RLS worse. So having been through that once, I really feel like it is my responsibility to examine this in more detail just so we do not make the same mistake again."

The *Mayo Clinic* paper concludes, "A number of opioid medications in low dose appear effective in refractory RLS. The risks of opioid use are relatively low, taking into account the much lower doses used for RLS compared with those in patients with pain syndromes. As long as reasonable precautions are taken, the risk-benefit ratio is acceptable and opioids should not be unreasonably withheld from such patients." **SR**

Lisa Spear is associate editor of Sleep Review.

questionnaire. The researchers then follow up with them every 6 months with surveys online. Data collected pertains to opioid medication, dose, severity of symptoms, opioid side effects, sleep quality, and augmentation.

So far, "Opioids appear to be effective, long-term, without dose escalation, they are well-tolerated, and we use them only in cases in which people developed augmentation and don't respond to

MAYO CLINIC

CONSENSUS RECOMMENDATIONS

The Appropriate Use of Opioids in the Treatment of Refractory Restless Legs Syndrome

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Abstract

Restless legs syndrome (RLS) is a distinct disorder, differing from chronic pain in many ways. Refractory RLS is characterized by unresponsiveness to dopamine agonists or alpha-2-delta ligands due to inadequate efficacy, augmentation, or adverse effects. This may result in severely impaired quality of life, profound insomnia, and suicidal depression. Opioid therapy is a mainstay in the management of these patients. This article summarizes the basic science and clinical evidence in support of their use, including the positive result of a large controlled multicenter study of 306 subjects, and outlines an approach to their use in clinical practice. Treatable explanations for RLS refractoriness, such as low iron stores, and other therapeutic options, such as combination therapy, should be considered before prescribing opioids. The agents most commonly used are oxycodone and methadone, but tramadol, codeine, morphine, and hydrocodone can also be considered. Controlled-release medication should be used for evening dosage and short-acting drugs, if needed, during the day. Effective doses are considerably lower than used for chronic pain (oxycodone 10-30 mg daily; methadone 5-20 mg daily) and the risk of opioid use disorder is relatively low. However, sensible precautions should be undertaken, including assessing opioid risk with standard questionnaires, using an opioid contract, using urine drug screens, consulting state prescription drug monitoring programs, and frequent reevaluation of effectiveness and side effects. Opioid use in selected patients with refractory RLS may be life-transforming with favorable risk-benefit ratio.

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Restless legs syndrome (RLS) is a common disorder, with about 2% of the population afflicted with symptoms occurring at least twice a week and resulting in moderate or severe distress.[1,2] Most patients obtain at least initial relief with first-line agents, specified as dopamine agonists (pramipexole, ropinirole, rotigotine patch) and alpha-2-delta ligands (gabapentin, gabapentin enacarbil, pregabalin).[3] However, adverse effects prevent their use in some patients and the therapeutic effect can wear off with time. Importantly, as many as 50% to 70% of patients using dopamine agonists develop drug-induced augmentation over 10 years,[4,5] characterized by earlier symptom onset, involvement of arms and trunk, and shorter duration of relief from treatment. When RLS becomes unresponsive to monotherapy with first-line agents of both classes due to inadequate efficacy, augmentation, or adverse effects, it is considered refractory to treatment.[3]

The worsening epidemic of prescription and illicit opioid abuse has made many caregivers wary of prescribing opioids. Current consensus is that opioids have only a limited role in the management of chronic pain in the absence of malignancy or end-of-life care.[6] In contrast, published clinical trials and case series demonstrate the considerable effectiveness of opioids in treating refractory RLS, a distinct disorder with a different etiology, pathophysiology, and epidemiology from chronic pain syndromes.[7] Differentiating features of the disorder include the identification of several risk alleles by genomewide association studies, brain iron deficiency, and abnormalities in the dopamine system. Despite this, patients with RLS frequently report

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difficulty obtaining opioid prescriptions from providers.

The aim of this article is to summarize the basic science and clinical evidence supporting the use of opioids for the treatment of refractory RLS and to outline a responsible approach to their use. It is our opinion that the risk-benefit ratio of opioid use in patients with RLS who are selected according to our guidelines is positive and that risk can be minimized as long as reasonable precautions are followed.

CLINICAL NEED

Refractory RLS is a common clinical problem. The following case scenario illustrates a typical patient with RLS refractory to first-line therapies who is an excellent candidate for opioid therapy.

A 59-year-old woman with a family history of RLS in her father and brother presented with worsening RLS symptoms over 25 years. Pramipexole had been prescribed 15 years previously at a time when her symptoms occurred only after going to bed, delaying sleep onset by an hour. Initially a dose of 0.25 mg taken 2 hours before going to bed gave full relief. As time passed, symptoms began earlier in the day and eventually started whenever she sat down after 1 PM, also occurring in her arms. The dose of pramipexole had been increased to 1 mg daily. Pramipexole was discontinued a year before presentation and a rotigotine patch was substituted at 3 mg daily. Initially this was effective but over several months the effect wore off with recurrence of symptoms during the day and night, persisting after withdrawal of the drug. Pregabalin 300 mg in the evening failed to control symptoms adequately and caused feelings of depression. She did not snore and was not obese. Serum ferritin level was 135 μg/mL and transferrin saturation was 27%. At the time of presentation, the patient was sleeping only 3 hours a night and could not sit down without symptoms after 1 PM.

PRECLINICAL STUDIES: OPIOID PATHOPHYSIOLOGY IN RLS

Opioid medications stimulate G-protein–linked mu, kappa, delta,[8] and opioid receptor like-1 receptors,[9] which are found throughout the nervous system, especially in the spinal cord, brainstem, and thalamus. These are preserved throughout evolution, and serve other purposes in addition to their overt human clinical role in analgesia. Pathophysiologic understanding of RLS is incomplete and likely multifactorial.[7] Major clues include therapeutic responses, most specifically with dopaminergics, iron, and opioids. Other lines of research demonstrate abnormalities in iron, dopamine, hypocretin, opioid, and glutamatergic systems, and peripheral nerve sensory processing.

In a postmortem study evaluating opioid pathology,[10] 5 brains from patients with RLS and 6 brains from controls without other neurological disease were stained with antibodies for beta-endorphin, met-encephalin, and leu-encephalin, and cell numbers counted in a blinded fashion. In the thalamus, beta-endorphin–positive cells were reduced by 37.5% (P=.006; effect size, 2.16), and met-encephalin cells by 26.4% (P=.028; effect size, 1.58) in patients with RLS compared with controls but there was no difference in leu-encephalin cells. In the substantia nigra, there were no differences in beta-endorphin, met-encephalin, or leu-encephalin. Tyrosine hydroxylase staining for dopamine cells was normal. RLS pathology in the thalamus is also implicated by voxel-based magnetic resonance imaging studies, which inconsistently show increased pulvinar size,[11,12] reduced single-photon emission computerized tomography scan *N*-acetylaspartate:creatine ratio and *N*-acetylaspartate concentrations in the medial thalamus,[13] and functional magnetic resonance imaging studies, which show increased activity in the thalamus and cerebellum while RLS symptoms are present. Although these studies do not specifically implicate opioid systems, opioid receptors are very abundant in the thalamus.

Daytime positron emission tomography imaging using the nonspecific opioid ligand [11C] diprenorphine did not differentiate between human RLS and controls. Correlations were, however, found between mu-receptor–binding potential in amygdala, medial thalamus, anterior cingulate, and orbitofrontal cortex and RLS subjects' reported severity as measured by the International RLS Study Group severity scale.[14] These 4 regions have been shown to have varying degrees of interconnection and are associated not only with emotion and reward in decision making but

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also with addiction, impulsivity, and anxiety.[15] Decreased binding suggests either increased endogenous opioid receptor occupancy or downregulation/internalization of the receptors.

There is evidence supporting opioid interactions with dopaminergic systems on the basis of *in vitro* and clinical data. Stimulation of opioid receptors, especially mu receptors, which are robustly associated with dopamine receptors, can facilitate dopamine release as demonstrated by microdialysis studies in mice and on functional imaging of dopamine receptor occupancy in humans.[16,17] Importantly, pretreatment of RLS with a dopamine antagonist will negate any benefit of opioids, also suggesting that opioids interact with or work via dopaminergic systems to treat RLS.[18] If naloxone, an opioid antagonist, is given to untreated subjects with RLS, no overt effect is seen,[19,20] but if given in a double-blind fashion to opioid-treated patients with RLS, the RLS signs and symptoms reappear, suggesting that naloxone blocks the beneficial effects of the opioid agonist.[21,22] However, naloxone does not block the beneficial effects of a dopamine agonist, suggesting that the dopaminergic response is not mediated via an opioid mechanism.[23]

CLINICAL STUDIES

Despite how long opioid drugs have been used for RLS, there are few high-quality, placebo-controlled studies to support their use. A parallel-group study randomized 306 patients with moderate to severe RLS and previous unsuccessful treatment to receive flexibly dosed prolonged-release oxycodone/naloxone or placebo.[24] After 12 weeks, oxycodone/naloxone resulted in a greater symptom reduction than placebo as found using the International Restless Legs Syndrome Scale[25] (−8.15; 95% CI, −10.85 to −5.46), with a mean dose of oxycodone of 21.9±15.0 mg and that of naloxone of 11.0±7.5 mg. The Clinical Global Impression responder rate was significantly higher in the oxycodone/naloxone group (67%) than in the placebo group (35%). Sleep adequacy and quantity improved more in the oxycodone/naloxone group than in the placebo group as measured by the Medical Outcome Studies sleep subscales. Daytime somnolence was not different between groups. During a subsequent 40-week open-label phase involving 197 subjects, oxycodone/naloxone was titrated from 5 mg oxycodone twice daily to a maximum of 40 mg twice daily. Forty subjects discontinued therapy, including 6 because of lack of therapeutic effect and 21 because of adverse events. At the end of the 40 weeks, the mean daily oxycodone dose was 18.1±10.5 mg. Efficacy was maintained with a reduction in the International Restless Legs Syndrome Scale score from onset of the open-label phase. Drug withdrawal symptoms were noted in only 3 of 176 subjects. Prolonged-release oxycodone/naloxone is approved for the treatment of RLS in more than 20 European countries, including the United Kingdom, France, and Germany.

A small double-blind crossover study randomized 11 patients with moderate to severe RLS to receive oxycodone in divided doses (2 hours before and at bedtime) or placebo. On self-rated 0 to 4 scales, oxycodone (mean dose of 15.9 mg/d) improved RLS symptoms of motor restlessness and leg paresthesia better than placebo.[26] A retrospective long-term study of various opioids in refractory RLS showed that 20 of 36 continued on opioid monotherapy (mean, 5 years and 11 months) and only 1 patient discontinued because of the development of tolerance and addiction.[27]

Two open-label studies support the effectiveness of the chronic use of methadone for refractory RLS. One study evaluated 27 subjects who failed on average 5 or more previous treatments for RLS.[28] Seventeen remained on methadone for 23±12 months at a dose of 15.5±7.7 mg (range, 5-40 mg) and reported continued benefit and tolerability. Most patients who stopped methadone did so in the first month of therapy. Another longitudinal study reported on a consecutive series of 76 patients on methadone with primary RLS and complete data between 1997 and 2007.[3] Unlike dopamine agonist treatment, the long-term tolerability was excellent, without any evidence of augmentation. The median daily dose after 6 months of treatment was 10 mg. This did not increase in the first 3 years of use but did increase by a median of 5 mg and a maximum of 10 mg in those patients who had been followed for 4 to 7 years. No one who took methadone for at least a year subsequently discontinued it.

Methadone is frequently used to treat narcotic addiction because it has less abuse potential than do other narcotics.[29] In contrast to morphine and most other narcotics, its use does not cause intracellular forskolin-stimulated cyclic adenosine monophosphate accumulation, a mechanism thought to contribute to opioid tolerance.[30] Methadone also uniquely antagonizes *N*-methyl-D-aspartate receptors in the spinal cord,[31] an area heavily implicated in RLS symptom genesis.[32,33] Therefore, although there is no human clinical comparison of different opioid medications, there is scientific rationale to specifically support the use of methadone, especially when long-term treatment is required.

USING OPIOIDS FOR THE TREATMENT OF RLS

Indications

Restless leg syndrome is considered refractory to treatment when it is unresponsive to monotherapy with tolerable doses of first-line agents of both classes (dopamine agonists and alpha-2-delta ligands) due to inadequate efficacy, augmentation, or adverse effects.[3] Doses of dopamine agonists should generally not exceed those recommended to prevent the development of augmentation.[34] Before considering opioid therapy, physicians should consider other alternative approaches.[34]

1. Is there evidence for low systemic iron stores (serum ferritin concentration of <75 μg/mL)? Oral or intravenous iron therapy may relieve symptoms without the need for additional medications.[3,35]
2. Have other factors that might exacerbate RLS been considered, such as the use of drugs that can worsen symptoms, including antihistamines, serotonergic antidepressants, and dopamine antagonists, or the presence of other sleep disorders such as obstructive sleep apnea?
3. Has combination therapy been considered, using lower doses of agents of different classes? In patients with severe symptoms this may not be appropriate and in some patients with profound RLS associated with dopamine agonist augmentation, opioids may be indicated even if alpha-2-delta agents have not had an adequate trial.
4. In the case of dopamine agonist augmentation, has a 10-day washout period, without immediate substitution of an opioid, been considered? Although this may allow determination of the severity of baseline symptoms off all drugs, an exacerbation of RLS with profound insomnia very frequently develops during the washout period and this approach is appropriate only for some carefully selected patients.

Not all these options may be relevant or appropriate in every patient. The time of initiation of opioid therapy depends on many factors, including the severity of the symptoms and their effect on sleep and quality of life. Although the benefits and risks should be carefully weighed, appropriate patients should not be deprived of opioids simply because of fear of opioid use disorder.

Precautions

Physicians are increasingly reluctant to prescribe long-term opioids because of recent heightened scrutiny by regulatory agencies and increased concerns of high rates of addiction and overdose recently publicized by organizations such as the Centers for Disease Control and Prevention.[6] However, as long as reasonable precautions are taken, this should not deter physicians from prescribing medications necessary for the health of their patients. Refractory RLS can be a devastating condition, resulting in profound insomnia, suicidal depression, and severely compromised quality of life.[36] Nevertheless, prescribers should act responsibly with an understanding of the opioid epidemic afflicting the United States and the legal requirements of individual states. Following simple standardized safety practices reduces risk to patients, allowing for effective use of the drugs (Table 1). Several guidelines for chronic opioid use for pain with evidence in support of the recommendations have been published, including examples of patient questionnaires and contracts.[6,37-39]

Before initiating opioid therapy, patients should be questioned about a personal or family history of alcohol or drug abuse (including prescribed medications), and present and past psychiatric disease. These factors increase the risk of opioid dependence, which is also higher in men and younger patients. Screening questionnaires

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TABLE 1. Summary of Considerations in the Use of Opioids for Refractory RLS

1. Opioids should be considered for the treatment of RLS that is not adequately controlled with first-line agents due to poor response, adverse effects, or, in the case of dopamine agonists, augmentation.
2. Factors that may be responsible for an inadequate response, especially low iron stores, the use of medications that can exacerbate RLS, or obstructive sleep apnea, should be considered.
3. Alternative approaches should be considered when relevant, including using combination therapy of nonopioid agents or, in the case of dopamine augmentation, a 10-day washout period before substituting an opioid. These approaches are not appropriate for all patients.
4. Before initiating opioid therapy, patients should be assessed for risk of opioid use disorder, state prescription drug monitoring programs should be queried, and a urine drug screen performed.
5. Patients should be informed about expectations of treatment and the risks of opioids.
6. Patients should be asked to sign an opioid contract, including at a minimum the following:
   - An understanding of the side effects of opioids and the risk of opioid use disorder;
   - That medications should be obtained from only a single provider and a single pharmacy;
   - That early refill prescriptions will generally not be issued even if the medication is reported lost;
   - That the dose should not be altered by the patients without discussion with the prescribing physician;
   - That medication should not be shared with anyone else.
7. Regular follow-up is needed, assessing effectiveness of therapy, side effects, and evidence for development of opioid use disorder. State prescription drug monitoring programs should be assessed regularly and a urine drug screen considered at least once annually, especially in high-risk patients.
8. Testing initial response with a short-acting drug is reasonable, but long-acting or extended-release agents are preferred at night, with either short- or long-acting agents added during the day as needed.
9. Treatment should commence with low doses, increasing as needed and tolerated, but the individual risk-benefit ratio should be carefully considered if doses above those listed in Table 2 are used, because such doses have been associated with increased overdose-related mortality.
10. The choice of drug to be used depends on physician preference, patient factors, and cost, but the prescriber should be very familiar with dosing schedules and the individual differences between agents.
11. Care should be taken with dosages when transitioning a patient between different opioids due to varying drug potencies and cross-tolerance.

RLS = restless leg syndrome.

for depression and anxiety may be helpful, and validated tools are available to stratify risk, such as the Opioid Risk Tool[40] and the revised Screener and Opioid Assessment for Patients with Pain.[41] Opioids should not necessarily be withheld in patients at higher risk but more intensive monitoring may be needed.

Alternative therapies should be discussed with the patient, and the reasons for an opioid prescription should be documented in the medical record. Treatment aims should be specified and tailored to the patient's primary complaint related to RLS, such as inability to initiate sleep at night. It should be emphasized that complete relief of symptoms is not a realistic long-term goal in most patients. The goal should be to reduce symptoms to a level that provides sustainable improvement in sleep and overall quality of life. Potential adverse reactions should be described, including nausea, constipation, pruritus, myoclonus, drowsiness, and cognitive impairment. The possibility of precipitating or exacerbating obstructive or central sleep apnea, or the conversion of treated obstructive sleep apnea to central sleep apnea, should be considered. Opioids should not be taken together with alcohol and preferably not together with benzodiazepines. An electrocardiogram to assess the QT interval should be obtained before prescribing methadone and should be repeated after initiation of the drug, particularly when it is combined with other agents that may cause QT prolongation.

An opioid contract should be signed by each patient.[6] This should include an understanding of the risk of opioid use disorder, that medications should be obtained from only a single provider and a single pharmacy, that early refill prescriptions will generally not be issued even if the medication is reported lost, that the dose should not be altered by the patients without discussion with the prescribing physician, and that medication should not be shared with anyone. The patient should

TABLE 2. Suggested Doses for Using Opioids in RLS

Drug	Starting total daily dose	Usual effective total daily dose
Tramadol (immediate or extended release)	50 mg (100 mg ER)	100-200 mg
Codeine	30 mg	60-180 mg
Morphine CR	7.5-15 mg	15-45 mg
Oxycodone (immediate or extended release)	5-10 mg	10-30 mg
Hydrocodone (immediate or extended release)	10-15 mg	20-45 mg
Methadone	2.5-5 mg	5-20 mg

CR = controlled release; ER = extended release; RLS = restless leg syndrome.

be informed that state prescription drug monitoring programs will be interrogated. A urine drug screen can be performed before initiation of therapy, especially if there is suspicion of existing opiate use. Patients should be reassessed at regular intervals, usually every 3 to 6 months, to determine efficacy, side effects, and any evidence for opioid use disorder or misuse. In particular, practitioners should consider whether patients with multiple comorbid conditions may have supplies of opioids prescribed in the past for other disorders.[42] The prescription drug monitoring program data should be checked at each visit and random urine drug screens considered at least once yearly, especially in higher risk patients. The goals of urine drug screens are to determine whether the patients are taking any other unsuspected narcotic substance and to show that the patient is taking the prescribed opioid and not diverting it. Screens differ in the list of drugs tested, and physicians should familiarize themselves regarding which drugs are included in the specific screen ordered. In particular, assessment for tramadol or methadone may need to be specially requested. The interpretation of drug screens is complex and unexpected results should be discussed with the toxicologist or the laboratory performing the test before conclusions are reached. At follow-up visits, patients should be reassessed for the development of depression and anxiety and appropriately treated or referred.

Drugs and Doses

Most published studies of opioids in RLS have used oxycodone or methadone.[24,26-28] There has been experience with other agents[27] but no comparative studies have been reported. Although lower potency drugs such as codeine or tramadol can be tried,[27,43] most patients with refractory symptoms will require the use of high-potency medications. Testing initial response with a short-acting opioid may be a reasonable initial option but in general, longer-acting and controlled-release drugs are preferred. This may be especially important at night, because short-acting opioids may not give adequate length of coverage and may be associated with end-of-dose rebound of RLS symptoms. However, shorter-acting drugs may be appropriate during the day when symptoms may be less severe, because lower doses can be used. Choice of a specific drug depends on individual prescriber and patient factors, including cost of medication.[44] Low doses should be given initially with titration to usual effective doses on the basis of efficacy and side effects. The timing of doses depends on symptoms: the first objective should be to give relief at night but some patients will require additional daytime doses. The goal should be to improve patient's quality of life but not to necessarily eliminate all RLS symptoms. Total daily doses above those listed in Table 2 may sometimes be needed, but the risk-benefit ratio should be carefully assessed because such doses have a significantly increased risk of overdose-related deaths in studies of patients with chronic noncancer pain.[45-47]

In an attempt to simplify the available choices, this article will restrict discussion to only a few of the more commonly used agents. Methadone is anecdotally considered to be the most effective opioid for RLS, but has variable pharmacokinetics and pharmacodynamics, is long acting, may cause prolongation of the electrocardiogram QT interval at high doses,[48] and reduce testosterone levels. Practitioners

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prescribing methadone should be knowledgeable about these unique features. Extended-release oxycodone is frequently used but similar medications include controlled-release morphine. Tramadol carries a risk of seizures particularly when the patient is also taking antidepressants. There is anecdotal evidence that tramadol may cause augmentation.[49-51] Table 2 lists the recommended initial and usually effective dose ranges but it should be noted that a minority of patients may require higher doses than those listed to obtain relief from symptoms. These doses are derived from limited published studies, anecdotal experience, and the approximate equivalence in strength of different agents.

It is important to emphasize that the doses of opioids used for refractory RLS are far lower than those used for the treatment of chronic pain syndromes. These lower doses markedly reduce the risk of opioid use disorder. In a study of nationwide US medical and pharmacy claims to Blue Cross and Blue Shield insurance companies in 2015, the rate of opioid use disorder in patients taking low-dose opioids for more than 90 days was 6/1000 patients, compared with 40/1000 patients using high-dose opioids, an almost 7 times lower frequency. Low-dose opioids were defined as less than 100 mg morphine or equivalent per day, an upper limit far higher than that recommended for RLS, suggesting that the rate of opioid use disorder in patients with RLS may be even lower.[52]

Unresolved Clinical Questions

Further well-designed research studies are needed to resolve a number of clinical questions. The comparative effectiveness and side effects of different opioids in patients with refractory RLS need to be determined. Studies are needed to confirm the clinical impression that maintaining a low dose of a dopamine agonist or alpha-2-delta ligand may allow a lower dose of opioid to be used. Further long-term studies of safety and efficacy are needed. In particular, larger studies are needed to assess the risk of dose escalation and abuse of opioids prescribed for RLS.

There is no consensus on how to convert patients with refractory RLS from a dopamine agonist or alpha-2-delta ligand to an opioid.[34] One choice is to titrate the opioid to a therapeutic level and then slowly wean and discontinue the preexisting medication. However, in patients with severe augmentation, an alternative approach is to first taper down the previous drug before introducing an opioid. This allows evaluation of baseline symptoms off medication but often leads to transitory extremely severe RLS symptoms during the washout period. These varying approaches need to be systematically compared.

CONCLUSION

In summary, a number of opioid medications in low dose appear effective in refractory RLS.[5] The risks of opioid use are relatively low, taking into account the much lower doses used for RLS compared with those in patients with pain syndromes. As long as reasonable precautions are taken, the risk-benefit ratio is acceptable and opioids should not be unreasonably withheld from such patients.

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Abbreviations and Acronyms: **RLS** = restless legs syndrome

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Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

CDC Newsroom

Some policies, practices attributed to the Guideline are inconsistent with its recommendations

Media Statement

Embargoed Until: Wednesday, April 24, 2019, 5 PM, EDT
Contact: Media Relations
(404) 639-3286

In a new commentary in the *New England Journal of Medicine (NEJM)*, authors of the 2016 *CDC Guideline for Prescribing Opioids for Chronic Pain* (https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fmmwr%2Fvolumes%2F65%2Frr%2Frr6501e1er.htm) (Guideline) advise against misapplication of the Guideline that can risk patient health and safety.

CDC commends efforts by healthcare providers and systems, quality improvement organizations, payers, and states to improve opioid prescribing and reduce opioid misuse and overdose. However, some policies and practices that cite the Guideline are inconsistent with, and go beyond, its recommendations. In the NEJM commentary, the authors outline examples of misapplication of the Guideline, and highlight advice from the Guideline that is sometimes overlooked but is critical for safe and effective implementation of the recommendations.

CDC is raising awareness about the following issues that could put patients at risk:

- **Misapplication of recommendations to populations outside of the Guideline's scope.** The Guideline is intended for primary care clinicians treating chronic pain for patients 18 and older. Examples of misapplication include applying the Guideline to patients in active cancer treatment, patients experiencing acute sickle cell crises, or patients experiencing post-surgical pain.
- **Misapplication of the Guideline's dosage recommendation that results in hard limits or "cutting off" opioids.** The Guideline states, "*When opioids are started*, clinicians should prescribe the lowest effective dosage. Clinicians should... avoid *increasing* dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day." The recommendation statement does not suggest discontinuation of opioids already prescribed at higher dosages.
- **The Guideline does not support abrupt tapering or sudden discontinuation of opioids**. These practices can result in severe opioid withdrawal symptoms including pain and psychological distress, and some patients might seek other sources of opioids. In addition, policies that mandate hard limits conflict with the Guideline's emphasis on individualized assessment of the benefits and risks of opioids given the specific circumstances and unique needs of each patient.
- **Misapplication of the Guideline's dosage recommendation to patients receiving or starting medication-assisted treatment for opioid use disorder.** The Guideline's recommendation about dosage applies to use of opioids in the management of chronic pain, not to the use of medication-assisted treatment for opioid use disorder. The Guideline strongly recommends offering medication-assisted treatment for patients with opioid use disorder.

The Guideline was developed to ensure that primary care clinicians work with their patients to consider all safe and effective treatment options for pain management. CDC encourages clinicians to continue to use their clinical judgment, base treatment on what they know about their patients, maximize use of safe and effective non-opioid treatments, and consider the use of opioids only if their benefits are likely to outweigh their risks.

The Guideline includes guidance on management of opioids in patients already receiving them long-term at high dosages, including advice to providers to:

- maximize non-opioid treatment
- empathetically review risks associated with continuing high-dose opioids
- collaborate with patients who agree to taper their dose
- if tapering, taper slowly enough to minimize withdrawal symptoms
- individualize the pace of tapering
- closely monitor and mitigate overdose risk for patients who continue to take high-dose opioids

Patients may encounter challenges with availability and reimbursement for non-opioid treatments, including nonpharmacologic therapies (e.g., physical therapy). Efforts to improve use of opioids will be more effective and successful over time as effective non-opioid treatments are more widely used and supported by payers.

CDC developed the Guideline to be practical and created clinical tools to help primary care providers help patients manage pain more effectively and safely, while mitigating the potential risks of prescription opioids when needed. CDC has also created specific resources on tapering, dosage, and appropriate application of the Guideline such as:

- Pocket Guide: Tapering Opioids for Chronic Pain (https://www.cdc.gov/drugoverdose/pdf/Clinical_Pocket_Guide_Tapering-a.pdf) is a quick-reference tool for when and how to taper and important considerations for safe and effective care.
- CDC Opioid Prescribing Guideline Mobile App (https://www.cdc.gov/drugoverdose/prescribing/app.html) is designed to help providers apply the recommendations of the Guideline in clinical practice. It features a morphine milligram equivalent (MME) calculator, summaries of key recommendations, motivational interviewing techniques, resources, and a glossary.
- Applying CDC's Guideline for Prescribing Opioids Series (https://www.cdc.gov/drugoverdose/training/online-training.html) is an interactive, web-based training featuring 11 self-paced learning modules with case-based content, knowledge checks, and integrated resources to help providers gain a deeper understanding of the Guideline.

CDC continues to help inform and improve clinicians' ability to offer safer, more effective care based on the best available science. As part of that process, CDC is evaluating the adoption, use, and public health impact of the Guideline and its related resources.

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (http://www.hhs.gov/)

CDC works 24/7 protecting America's health, safety and security. Whether disease start at home or abroad, are curable or preventable, chronic or acute, or from human activity or deliberate attack, CDC responds to America's most pressing health threats. CDC is headquartered in Atlanta and has experts located throughout the United States and the world.

Page last reviewed: April 23, 2019

Centers for Disease Control and Prevention
Sleep and Sleep Disorders Funding Request
FY 2020 Funding Request

Background

Sleep is a significant public health issue. Healthy sleep impacts nearly every system of the body and the progression of many conditions. Moreover, sleep disorders are responsible for a litany of health and safety issues, and some of these conditions are easily identified and managed with proper awareness and education. While the Centers for Disease Control and Prevention (CDC) is tasked with addressing major public health threats and taking on activities that improve health and lower healthcare costs, CDC currently does not have a comprehensive sleep initiative.

Until the end of 2018, CDC had been supporting the National Healthy Sleep Awareness Project (NHSAP). This effort was valuable from a public health standpoint and highly-regarded by the sleep community. Ultimately, NHSAP facilitated a number of successful awareness campaigns, surveillance activities, and professional publications.

CDC had supported NHSAP with discretionary resources for over five years and ended the project for FY 2019 citing a lack of dedicated funding. Sleep health aligns well with CDC's mission and public health efforts for sleep are as timely and relevant as similar efforts on obesity and smoking cessation. A sleep program at CDC will save and improve lives while lowering healthcare expenses.

Request

Please provide CDC's National Center for Chronic Disease Prevention and Health Promotion with a specific funding level of $250,000 for public health activities focused on sleep and sleep disorders.

Justification

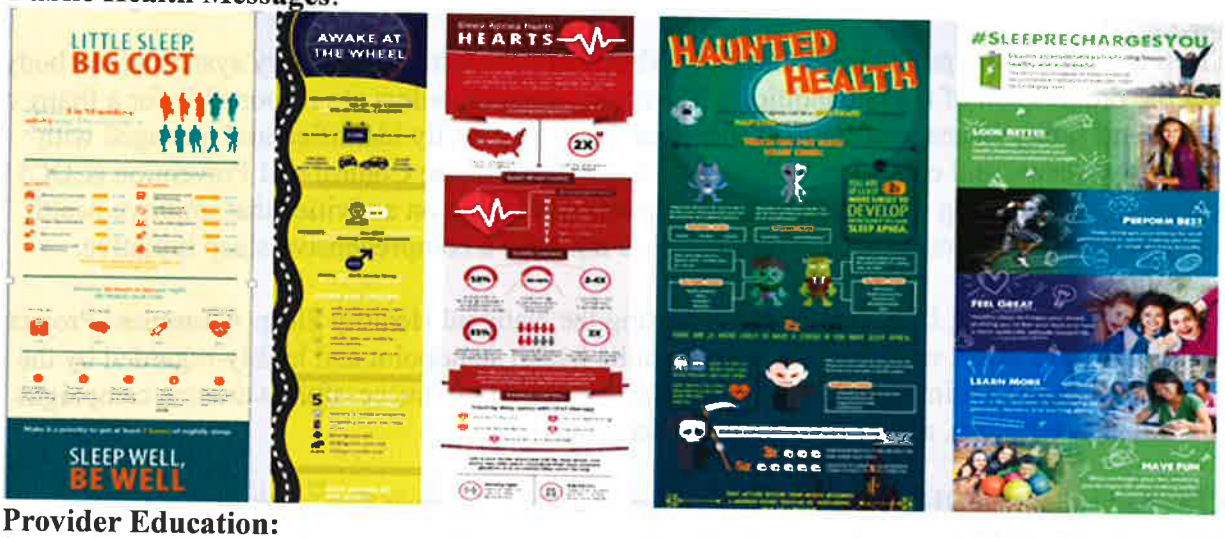
- When NHSAP was operating, it generated a notable return on investment and facilitated meaningful progress in a number of areas. Reinvigorating CDC sleep activities at this time will ensure that the public health advancements made under NHSAP are not lost and that emerging opportunities can be capitalized on.

- Due to the ongoing investment in sleep and forgotten sleep disorder research at NIH, DOD, and VA, there have been a number of recent breakthroughs in sleep research. An active sleep program at CDC will ensure scientific advancements are disseminated through professional education and public awareness to improve health outcomes.

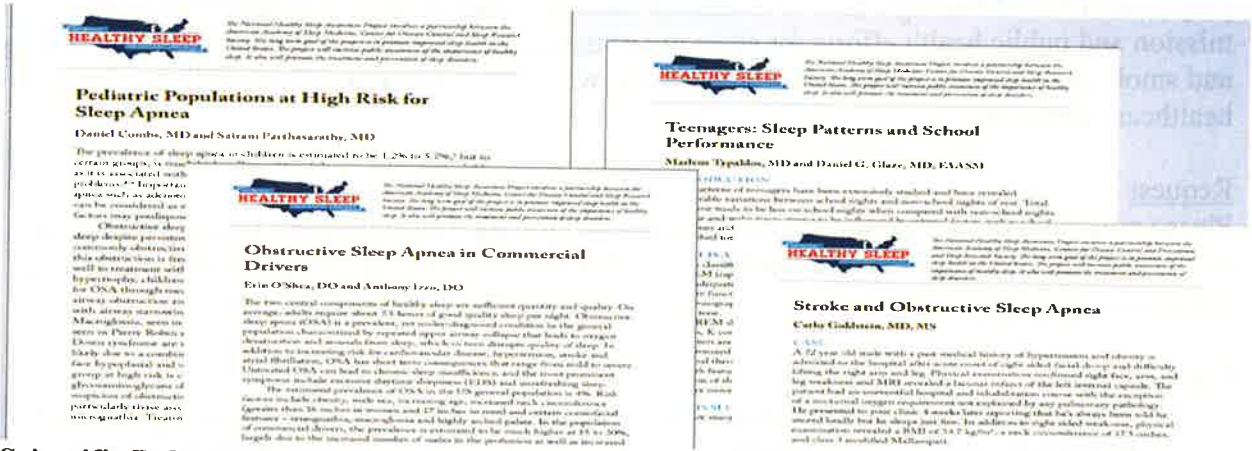
- The connections between disordered sleep and health issues, such as obesity, as well as public health challenges, such as drowsy driving are well-established. A robust CDC program with active community engagement will improve sleep health and address related healthcare issues.

National Health Sleep Awareness Project at CDC
Historical Overview & Successes Summary

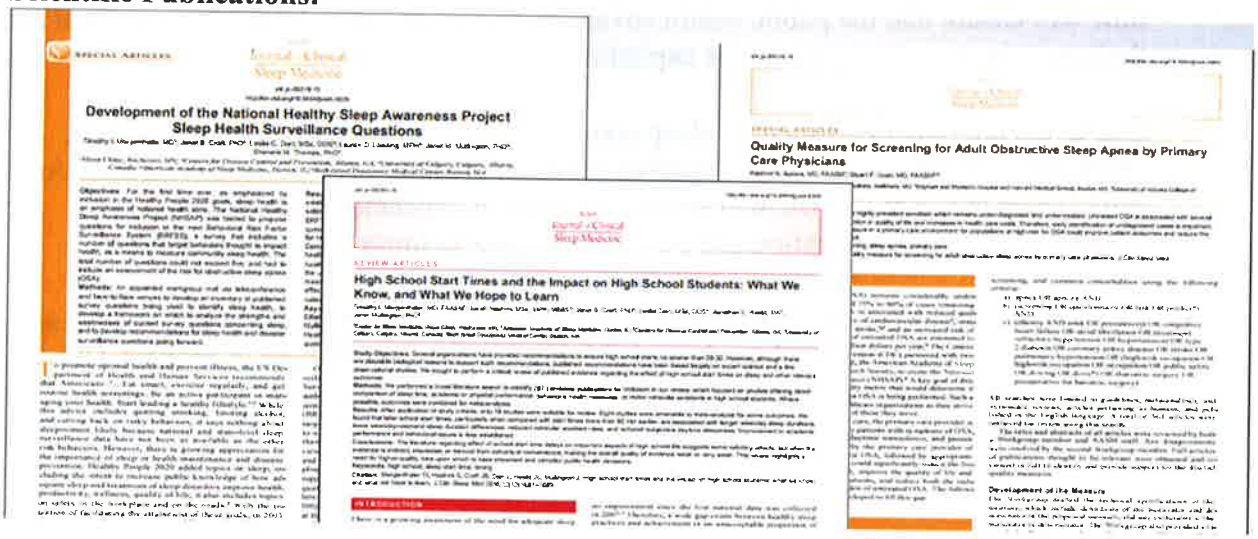
Public Health Messages:



Provider Education:



Scientific Publications:



Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Public Health Surveillance and Data

Millions of people (https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research) of all ages across the United States face the substantial and sometimes devastating consequences of neurological disorders and conditions.

In 2016, as part of the 21st Century Cures Act (https://www.congress.gov/bill/114th-congress/house-bill/6), Congress authorized Centers for Disease Control and Prevention (CDC) to initiate development of a **National Neurological Conditions Surveillance System (NNCSS)**. Congress has appropriated $5 million for the NNCSS as part of the FY 2019 spending bill for the U.S. Department of Health and Human Services.

How will the NNCSS work?

- The $5 million appropriated in FY 2019 will enable CDC to begin its NNCSS developmental and implementation work. This will include:
  1. Exploring data needs and identifying available data sources
  2. Determining how to build an effective system that will identify gaps in desired data and explore approaches
  3. Collaborating and communicating with partners, stakeholders, and Congress about the status and available details of the NNCSS.
- With this investment, consistent with the 21st Century Cures Act, the NNCSS will collect and synthesize data to help increase understanding of neurological disorders and to support further neurologic research.
- There will be **three stages** of the NNCSS, which CDC will carry out in association with partners and stakeholders:
  1. **Demonstrations** using two neurological conditions, multiple sclerosis (https://nccih.nih.gov/health/multiple-sclerosis) and Parkinson's disease (https://www.niehs.nih.gov/health/topics/conditions/parkinson/index.cfm), to determine how we can have the biggest impact by exploring innovative methods and complex data sources, and capturing lessons learned, to determine which approaches will help efficiently extend the NNCSS to other neurological conditions
  2. **Building out the NNCSS** for multiple sclerosis and Parkinson's disease using successful approaches from the demonstration projects, and checking methods, costs, and opportunities, as resources allow
  3. **Using lessons learned to extend the NNCSS** to other neurological conditions, as resources allow

CDC looks forward to helping to develop greater understanding of neurological disorders and conditions to improve health and economic consequences for those who are affected.

Page last reviewed: November 15, 2018