14th Annual NIH Pain Consortium Symposium on Advances in Pain Research

Pain Across the Lifespan

May 30-31, 2019

Masur Auditorium, NIH Clinical Center, NIH Main Campus

Revised July 1, 2019

This meeting summary was prepared by Lucas Smalldon, Rose Li and Associates, Inc., under contract to Infinity Conference Group. Review of earlier versions of this meeting summary by the following individuals is gratefully acknowledged: Silvia Paddock, Nancy Tuvesson.

Table of Contents

Acronym Definitions

Acronym Name	Acronym Definition
ADA	American Dental Association
AI	artificial intelligence
BA	bachelor's degree
BACPAC	Back Pain Research Consortium
BNST	bed nucleus of the stria terminalis
BRAIN	Brain Research through Advancing Innovative Neurotechnologies
CBT	cognitive-behavioral therapy
CD	cesarean delivery
CDC	Centers for Disease Control and Prevention
ChR2	channelrhodopsin 2
CNS	central nervous system
ED	emergency department
EPPIC-Net	Early Phase Pain Investigation Clinical Network
ERN	Effectiveness Research Network (Pain
fMRI	functional magnetic resonance imaging
FPRS	Federal Pain Research Strategy
HEAL	Helping to End Addiction Long-term
MDS	Minimum Data Set
MEPS	Medical Expenditure Panel Survey
MVC	motor vehicle collision
NHIS	National Health Interview Survey
NIDCR	National Institute of Dental and Craniofacial Research
NIH	National Institutes of Health
PAG	periaqueductal grey
PD	primary dysmenorrhea
PRISM	Pragmatic and Implementation Studies for the Management of Pain
SNI	spared nerve injury

Introduction

The NIH Pain Consortium, created in 2003, fosters collaboration across National Institutes of Health (NIH) Institutes and Centers involved in pain research. The NIH Pain Consortium held its 14th Annual Symposium ("the Symposium") on May 30 and 31, 2019, on the main NIH campus in Bethesda, Maryland. Researchers, government officials, advocates, and health care providers convened to learn about recent advances in pain research, discuss ongoing and future research efforts, and identify opportunities to improve the status quo.

This year's Symposium focused on the complex and unique challenges of managing pain at each stage across the lifespan. Panel sessions focused on pain in pediatric populations, middle-age, and pain management in older adults. The Symposium also focused on the pain management experience of patients from special populations. The symposium further featured a keynote address by Sir Angus Deaton and Dr. Anne Case of Princeton University, who presented their work indicating that lack of higher education may be linked to chronic pain and "deaths of despair" caused by drug overdose (especially from opioids), alcohol-related disease, and suicide.

Due to the ongoing opioid overuse crisis, the connection between chronic pain management and the opioid epidemic was a recurrent theme of this year's Symposium, similar to the 2018 Symposium. Dr. Francis Collins, NIH Director, presented an update on the NIH HEAL (Helping to End Addiction Long-term) Initiative, which provides researchers with unprecedented funding opportunities for research into pain and addiction to opioids. The HEAL Initiative, which receives $500 million per year, now involves 12 NIH Institutes and Centers leading 26 HEAL research projects. It has already released more than 40 funding announcements for fiscal year 2019 and coordinates its efforts with the Secretary of the United States Department of Health and Human Services, the Surgeon General, federal partners, local government officials, and communities.

Other presenters focused on the transition from acute to chronic pain in various special populations such as pregnant women and those who experience primary dysmenorrhea, as well as those who suffer from long-term disabilities or who have experienced trauma. Additional topics discussed at the Symposium included child migraine, risk factors for developing chronic pain among older adults, roles of professional organizations and of family caregivers in addressing the pain epidemic, and the U.S. government's Pain Management Best Practices Inter-Agency Task Force. The Symposium also featured a series of presentations by junior investigators nominated for the annual Mitchell Max Award.

See Appendix A for the full 2019 NIH Pain Consortium Symposium agenda.

Day 1 Meeting Summary

Welcome and Opening Remarks

Helene Langevin, MD, Director, National Center for Complementary and Integrative Health

The NIH Pain Consortium represents a broad effort across NIH Institutes and Centers to address the management and treatment of pain in all its forms. The need to do this diligently *across the entire lifespan* was the focus of the 2019 NIH Pain Consortium Symposium. During 2017, the NIH Pain Consortium, along with the Interagency Pain Research Coordinating Committee, published the Federal Pain Research Strategy (FPRS). The FPRS outlines a research funding approach designed to address knowledge gaps that adversely affect outcomes for pain patients. The FPRS prioritizes research efforts to (1) understand mechanisms of childhood chronic pain and (2) identify developmental periods and life states that convey risk for or protection against pain conditions. These priorities align with the Symposium's focus on pain across the lifespan and highlight the need to address the continuum of pain (i.e., preventing pain, managing acute and chronic pain, and preventing the transition from acute to chronic pain). The whole-lifespan approach to pain prevention and management requires treatments that patients can practice, or providers can administer, for extended periods without risk of tolerance, addiction, or other dangerous side effects.

Keynote Address: Pain and Opioids in an Epidemic of Mental and Economic Distress

Sir Angus Deaton, PhD, and Anne Case, PhD, Princeton University

Sir Deaton and Dr. Case have identified demographic patterns that appear to be similar for those patients experiencing increased pain and those patients that experience "deaths of despair" (i.e., deaths associated with drug use, suicide, and alcoholic liver disease). Because of this correlation, they have hypothesized that these two phenomena may stem from the same underlying factors. Specifically, pain may form a link between social factors, such as education, and deaths of despair. Sir Deaton and Dr. Case have leveraged the National Health Interview Survey (NHIS) and Gallup Daily Poll to examine the relationship between education and the joint rise of pain and deaths of despair. These data document increases in pain and in deaths of despair particularly among white non-Hispanic men and women without a bachelor's degree (BA). In general, average pain levels rise during middle age for all white non-Hispanic men and women. Yet for those without a BA the distribution curve has shifted markedly over the past two decades, such that average pain levels increase earlier in this population compared to the general public, potentially indicating the influence of a deeper factor. Those patients experiencing chronic pain report being less able to carry out activities of daily living and report more mental distress.

Pain, in addition to being more prevalent among those without a BA, is also more disabling for these individuals. For example, NHIS data from 2014 to 2017 show that among white non-Hispanics ages 25 to 74 who reported experiencing back, neck, or joint pain, significantly larger

fractions of respondents without a BA reported having difficulties socializing, shopping, relaxing, walking, and standing. Social isolation is an important factor underlying suicide. Moreover, age profiles representing pain prevalence among individuals without a BA appear to exhibit cohort effects. That is, pain self-reports among individuals without a BA in more recent generations have risen compared to those among the same demographic from previous generations. Sir Deaton and Dr. Case believe that these data reveal an ongoing process that has been slowly developing for decades, in which physical pain, social isolation, and deaths of despair are disproportionately and increasingly affecting white non-Hispanic Americans lacking a BA.

Further evidence suggesting that these are steady and long-term trends is that they continued unperturbed throughout the 2009 economic recession. The demographics of these trends are also closely related to those of the opioid epidemic. Sir Deaton and Dr. Case suggest that economic pressures causing social disintegration among white non-Hispanics without a BA explain the observed trend: Opportunities steadily worsen for whites without a BA, with younger birth cohorts faring worse than older cohorts.

Keynote Speakers Q&A

Chronic Pain and Education

Participants discussed whether chronic pain may prevent some individuals from obtaining a BA (e.g., if they are unable to comfortably sit still during university courses). Sir Deaton noted that he and Dr. Case have not explored that possibility in depth and remarked that although more people are enrolling in university degrees, fewer among those who enroll are finishing their degrees compared to past years. Pain may be connected to this phenomenon, although evidence supporting that hypothesis is currently unavailable.

The Influence of Exercise

Pain and lack of exercise often reinforce each other. It is possible for an individual who at first experiences relatively mild pain to later experience more severe pain due to a decrease in exercise frequency. However, Sir Deaton and Dr. Case's research has not focused on this aspect of pain prevalence. Instead, their focus has been on the joint crises of decreased economic security and lack of meaning that seem to be affecting the same demographic groups that are experiencing rising rates of pain and deaths of despair.

The Elements of Race and Ethnicity

One attendee asked Sir Deaton and Dr. Case to describe the role of race and ethnicity in their research. Dr. Case noted that their work began with a focus on suicide, and that, for reasons that are not well understood, white Americans commit suicide at significantly higher rates than racial and ethnic minorities. Prior to fentanyl's spread across the United States, deaths of despair among black and Hispanic Americans trailed those of whites significantly. Dr. Case noted that perhaps the overall trends among white non-Hispanic Americans will begin to apply to ethnic minorities as well. Future data are needed to assess this possibility.

The Partial Picture Provided by Unemployment Statistics

Some members of the audience were surprised by the apparent disconnect between historically low unemployment rates and historically high rates of deaths of despair. However, Sir Deaton stressed the importance of obtaining "good" employment, not merely employment as such. Indeed, a person who has secured a job that fails to provide financial security may well experience social, economic, and personal despair that is not reflected in any unemployment statistics.

The Potential Limitations of Self-Report Data

Whenever comparing self-report data across time periods (e.g., changes in self-reported pain), one must consider the possibility that factors other than pain itself, such as peoples' willingness to report their pain or their perceptions of what is painful, explain the observed shift. However, in this case, the changes in pain self-reports are correlated with changes in self-reports about, for example, socializing. Moreover, both of the matched trends are associated with the lack of a BA, and assuming that changes in pain self-reports are due to changes in attitudes or perceptions fails to explain these associations.

Panel Session: Pain in Pediatric Populations

Moderator: James A. Griffin, PhD, National Institute of Child Health and Human Development

Overview: Biopsychosocial Predictors of the Transition from Acute to Chronic Pain in Children and Adolescents

Tonya Palermo, PhD, University of Washington

All chronic pain was once acute pain. The transition involves a range of biopsychosocial factors. Results of studies conducted exclusively with adults may have limited generalizability, because they do not account for developmental or interpersonal factors that are unique to childhood. Findings from a study of pediatric patients with functional abdominal pain demonstrated that 35 percent of patients exhibited symptoms into adulthood. Almost half of these individuals reported at least one site of chronic nonabdominal pain at follow-up. Evidence indicates that early identification of pain in childhood is important for preventing developmental progression toward adult chronic pain and disability. More than 4.5 million children receive surgery in the United States annually, and half of children admitted after surgery have moderate-to-severe acute pain while in the hospital. A systematic review revealed that 20 percent of children who receive surgery report chronic postsurgical pain at 12 months post-operation.

Putative biopsychosocial factors underlying the transition from acute to chronic pain include (1) altered pain processing (e.g., changes in pain thresholds due to an altered strength of inhibitory pathways), (2) interpersonal/family factors, and (3) sleep deficiency. Some investigators have hypothesized that, regarding family factors, child variables such as sex, emotional symptoms, coping style, and age/developmental status may modulate the relationship between pain and functional disability. Moreover, while family and parental risk (e.g., history of pain in the family or parental response style) may influence child pain and disability, chronic pediatric pain may in turn have a negative influence on parents and the family. This bidirectional influence indicates a

potentially outsized role for family factors in the transition from acute to chronic pain. Also, adolescents with chronic pain exhibit heightened rates of insomnia, which is associated with poorer health-related quality of life and increased pain-related disability. Although daily pain does not predict nighttime sleep, nighttime sleep does seem to predict next-day pain, which could indicate that sleep disruption leads to increased pain, but not vice versa. Investigators are pursuing efforts to teach youth how to manage pain by learning new ways to think about pain and by changing pain-related behaviors.

Migraine in Youth: Building the Evidence Base and Discovering Mechanisms of Effective Treatment

Scott Powers, PhD, ABPP, FAHS, Cincinnati Children's Hospital

Approximately 80 percent of young people have experienced head pain by 15 years of age. Those among that group who have experienced five or more episodes of moderate-to-severe intensity throbbing or pounding head pain or head pain with associated symptoms, such as sensitivity to light and sound or nausea, are typically diagnosed with migraine (approximately 10 percent). Dr. Powers' team has studied chronic migraine, which is clinically defined as 15 or more headache days per month, in young people. They administered a combination treatment of amitriptyline with cognitive-behavioral therapy (CBT) and a control treatment of amitriptyline with an "attention-matched control" (i.e., headache education). Results showed that the drug-CBT combination therapy more effectively reduced frequencies of youth migraine than the attention-matched control therapy. Specifically, 86 percent of participants in the experimental condition reported at least a 50 percent reduction in headache days, compared to only 69 percent of participants in the control group. Outcomes continued to improve at further follow-up visits. By 1-year follow up, combination CBT-amitriptyline therapy led 9 out of 10 experimental patients to experience clinically meaningful improvement in headache days and quality of life. Because migraine trials that leverage CBT have demonstrated fairly rapid reductions in migraine frequencies, future studies might be designed to include a time-to-endpoint, rather than an a priori, time course. Using such an approach, investigators could potentially re-randomize participants mid-study to explore various adaptive treatment plans.

Dr. Powers' laboratory also conducted a study comparing the efficacy of amitriptyline and topiramate, the two drugs most commonly prescribed by pediatric neurologists, with placebo in the treatment of migraine. The investigators ended the trial early after interim analysis showed poor results, with no significant difference between groups in the primary outcome of reduced headache days compared to baseline. They had also conducted 10,000 simulations of the study based on different sets of outcomes and failed to obtain a single statistically significant positive clinical result. In reaction to these findings, the investigators posed two questions: (1) How do children and adolescents with migraine improve? (2) How can nonpharmacologic treatments for migraine be made more accessible? These two questions about mechanisms and accessibility are now the primary focus of research in pediatric migraine. Investigators are combining functional magnetic resonance imaging (fMRI) with conditioned pain modulation to explore the brain mechanisms underlying pediatric migraine. Results indicate that CBT increases connectivity between the bilateral amygdala and its various projections throughout

the cortex. Additional functional imaging studies have been performed using arterial spin labeling. Imaging studies of both kinds have hinted at potential mechanistic drivers underlying CBT's effectiveness in reducing headache days among pediatric migraine sufferers. Moreover, certain phenotypic traits such as efficiency of pain processing appear to predict suitability for CBT interventions.

From Mechanisms to Intervention: Central Pain Processes in Primary Dysmenorrhea

Laura Payne, PhD, University of California Los Angeles

Investigators have begun exploring whether central sensitization may play a role in transitions from primary dysmenorrhea (PD) to chronic pain. Central sensitization occurs when repeated pain activation decreases the stimulus thresholds required to induce pain sensations. Central sensitization plays a role in many clinical pain syndromes in both children and adults, such as musculoskeletal pain, headache, fibromyalgia, and rheumatoid arthritis, suggesting a plausible link between central sensitization and PD. Severe symptoms of PD affect at least 25 percent of women and girls, and PD is a leading cause of school and work absences. It is also the most common gynecological complaint. However, PD is a *recurrent*—not a chronic—pain condition. To probe the pain mechanisms underlying PD, investigators compared adolescent and young adult girls (aged 16 to 25) with and without PD across three laboratory visits, during which investigators measured their central sensitization by assessing pain thresholds as well as pain excitations and inhibitions during participants' menstrual, ovulatory, and mid-luteal cycling stages.

The results revealed significant changes in pain tolerance and excitation and inhibition across all of the menstrual cycle stages. However, although investigators discovered evidence of central sensitization—as measured by heat pain tolerance and heat task performance—they found no differences in pain excitation or inhibition across PD and control groups. Dr. Payne speculated that this could be due to one of three factors: (1) young participants' could have experienced too few PD episodes to induce central sensitization; (2) central sensitization may only develop among a specific subset of PD sufferers, which would have been obscured by a study design that lumped all PD sufferers together; and (3) perhaps the current assessment methods are incapable of capturing the relevant underlying indicators of central sensitization.

Another study now aims to identify biomarkers—including menstrual pain symptoms and pain responses, as well as brain imaging—associated with menstrual and non-menstrual bodily pain over a 2-year period. The study will characterize a cohort of girls, post-menarche and aged 14 to 18 years, using a range of self-reported menstrual pain levels. A pilot study has also assessed the efficacy of mind-body interventions (i.e., psychoeducation, mindfulness, coping skills, and decatastrophizing) among young women with moderate to severe PD. At 1-month follow up, 40 percent of participants had a clinically meaningful reduction in pain (i.e., a decrease of at least 2 numerical rating scale points); at 12-month follow up, the number had risen to 55 percent. Qualitative analyses of participant self-reports indicate that participants developed better coping abilities, which could explain the improved pain scale ratings, rather than objective decreases in nociception.

Studying the Transition from Acute to Chronic Pain After Traumatic Stress

Samuel McLean, MD, MPH, University of North Carolina at Chapel Hill

Traumatic experiences such as a motor vehicle collision (MVC) or sexual assault can trigger enduring neurobiological changes, leading to adverse posttraumatic neuropsychiatric sequelae. Investigators have traditionally categorized their trauma survivor studies using symptom-based syndromes such as "chronic pain" or "posttraumatic stress," meaning that these syndromes are typically studied separately. However, such syndromes are more indicative of medical specialty demarcations than trauma survivor experience. In fact, trauma survivors who suffer from these various syndromes share overlapping experiences and are characterized by a similar underlying neurobiology. Yet different research groups study outcome clusters such as pain and depressive symptoms by collecting different types of data based on different theoretical models. Thus, Dr. McLean's research group designed a study that leveraged emergency department (ED) visits by conducting longitudinal follow-up on individuals who enrolled in an ED after a traumatic event such as an MVC. Acute post-MVC pain typically affects many bodily regions, including ones that were unaffected by direct physical trauma. That is, collision characteristics are poor predictors of post-MVC pain outcomes: yet, individual characteristics mediated by central neurobiological mechanisms *do* predict pain outcomes. Investigators found that at 6 weeks post trauma, pain phenotypes exhibited by sexual assault victims resembled those among MVC sufferers. These similarities suggest that the specific tissue trauma plays a relatively minor role in chronic pain that develops following trauma.

Investigators have expanded their research based on these results, using animal models to reveal that prolonged exposure to elevated catecholamine and glucocorticoid levels causes long-lasting hyperalgesia through sensitization of primary afferent nerves. This effect appears related to a protein called FKBP5. Individuals with a genetic variant that causes elevated FKBP5 levels also exhibit elevated cortisol levels, and these individuals are more likely to develop chronic pain following traumatic stress. Mechanistically, FKBP5 binds to glucocorticoid receptors, reduces the receptor's cortisol-binding capacity, and prevents it from transporting cortisol into the cell nucleus. This disruption causes a net increase in cortisol levels. Dr. Sarah Linnstaedt and colleagues (2018) found an *FKBP5* allele that causes elevated FKBP5 levels and correspondingly increased cortisol levels, thus linking the specific allele to the development of posttraumatic chronic pain. Furthermore, McLean's group found that among MVC and sexual assault survivors, carriers of the at-risk *FKBP5* allele were, indeed, more likely to develop chronic pain. Although individuals with the normal *FKBP5* allele also exhibit elevated FKBP5 and cortisol after trauma, individuals with the at-risk allele exhibit *unchecked* increases in both FKBP5 and cortisol levels.

Panel Session Q&A

Prevalence and Importance of the At-Risk FKBP5 Allele

Approximately 20 percent of individuals carry the at-risk *FKBP5* allele. Although the allele is closely associated with the posttraumatic transition from acute to chronic pain, it is likely only

one component of a more complex system of interacting factors that influence the transition. Investigators believe that epigenetic factors such as methylation influence *FKBP5* expression.

Psychosocial Interventions for Postsurgical Pain

Dr. Palermo's research group has piloted pre- and postoperative psychosocial interventions, each lasting for 3 weeks and targeting factors such as reducing hospitalization anxiety, fostering coping skills, and improving sleep hygiene, which aim to forestall the transition to postsurgical chronic pain. Some fMRI results indicate patterns of amygdala overactivity that correlate in conditions such as depression, anxiety, chronic pain, and posttraumatic stress disorder, suggesting a potential link among such conditions, possibly with a psychosocial component.

History of Trauma and Its Relationship to Pain Syndromes

One participant asked Dr. Payne whether her group had investigated any potential interactions between history of trauma—especially sexual abuse—and PD symptoms. Dr. Payne noted that her group has measured trauma yet found no link between trauma and chronic pelvic pain. Dr. Powers also noted that his group has conducted case interviews that included questions about history of trauma, adding that the resulting data were too sparse to draw any conclusions about a potential relationship between trauma and pediatric migraine.

Focusing on the Transition from PD to Chronic Pain

Dr. Payne's study excluded any potential subjects with pain conditions aside from PD, and thus did not investigate comorbidities among PD sufferers. The goal was to help develop improved treatments for PD alone and avoid the chronic pain that it sometimes leads to by preventing the development of central sensitization.

Introduction of Junior Investigator Presentations

Helene Langevin, MD, Director, National Center for Complementary and Integrative Health

The NIH Pain Consortium Mitchell Max Award for Research Excellence honors Dr. Mitchell Max for his lifetime contributions to pain research. The award has been presented each year since 2009 to an outstanding junior investigator. Criteria for selecting finalists include the quality of poster abstracts, relevance of the work to advancing pain research, and significance of the scientific question addressed.

Delayed Onset of Neuropathic Pain in Aged Males After Peripheral Nerve Injury

Michael D. Burton, PhD, University of Texas at Dallas

By 2050, one-third of the U.S. population will be aged 65 or older. Given the already-high pain burden (the annual cost of chronic pain in the United States is estimated at $635 billion) it will become increasingly important to understand how aging influences bodily mechanisms of pain signaling. To study this, Dr. Burton and colleagues used animal models (Fischer 344-Brown Norway first generation hybrid rats) of spared nerve injury (SNI) to compare pain signaling phenotypes between adult (3 to 6 months old) and aged (22-26 months old) animals, all of which were male. Prior to this work, investigators knew that aging was linked with upregulation of inflammatory markers such as MHC class II, IL-6, and IL-1β in the central nervous system

(CNS), and Dr. Burton and colleagues wanted to explore how this immune system dysregulation associated with aging might influence pain states. The overall purpose of this research was to better understand the acute phase of neuropathic pain development in aged individuals and to identify pain plasticity mechanisms involved in the transition from acute to chronic pain.

The investigators hypothesized that the aged animals would exhibit a heightened pain response to the SNI compared to the adult animals. To test this, investigators used Von Frey filaments to assess the animals' mechanical hypersensitivity. Surprisingly, the adult animals showed a rapid and robust pain response, while the onset of mechanical hypersensitivity in aged animals was markedly delayed, slowly developing over the course of approximately 3 weeks, then reaching a hypersensitivity plateau. Cold allodynia tests yielded a similar pattern of results, with the aged animals showing a delayed onset in CNS pain hypersensitivity. Moreover, the aged rats never reached the level of pain intensity of the adult animals. To study the acute pain phase and its transition toward chronic pain, the investigators assessed mechanical hypersensitivity and cold allodynia at baseline, 3 days, 5 days, 7 days, 10 days, 14 days, and 21 days, and once per week thereafter up to a 56-day timepoint. Inflammatory dysregulation was most pronounced during the acute pain phase, making the initial timepoints of special interest to the investigators, who measured gene expression for the inflammatory markers IL-6, ATF4, and ATF6—and for SK2, a calcium-activated potassium channel—in the animals' spinal cords at days 5 and 56. The aged animals showed elevated IL-6 and SK2 expression at day 5 in comparison to the adult animals. However, investigators saw no significant differences in expression at day 56. Dr. Burton and colleagues are conducting follow-up studies to investigate the hypothesis that inflammation and dysregulated signaling may lead to a reduction in self-care behaviors in the elderly, which in turn may lead to additional morbidity and increased mortality.

Questions

Dr. Burton and colleagues believe that the inflammation and the dysregulated signaling via SK2 channels are independent processes operating in parallel. However, they are now planning to conduct experiments inhibiting IL-6 expression to determine potential effects on SK2 signaling.

Autonomous Pain Recognition in Critically Ill Patients

Parisa Rashidi, PhD, University of Florida

Nearly 50 percent of critical care patients experience significant pain, and pain assessment is a critical component of pain management. Pain assessment is often difficult, particularly among nonverbal critical care patients. Providers typically use behavioral pain scales, but these must be administered manually and sporadically. Moreover, the scales are largely subjective and cannot characterize pain in relation to other assessments. Dr. Rashidi and colleagues are pioneering a novel approach to pain recognition and assessment in critically ill patients leveraging artificial intelligence (AI) technology. Their long-term goal is to combine AI with sensing technology to specify pain intensity in an autonomous, granular, objective, contextualized, and continuous manner. Their research has two primary functional aims: (1) pain expression recognition, and (2) activity recognition. Pain expression recognition can be achieved by recognizing a patient's facial expression and physical activity simultaneously, while

activity recognition can provide a means for automated pain contextualization in terms of patient function. The investigators will recruit 200 patients and capture granular data on facial expressions and body movements for up to 7 days using Shimmer3 sensors along with color and depth cameras. The resulting data, which are complex and high-dimensional, will be processed using deep learning models that will analyze the frames captured by sensors and cameras to deliver clinical indices measuring both pain and physical function.

Thus far, Dr. Rashidi and colleagues have collected data from approximately 22 patients. The results consist of more than 16 million video frames of patient posture, more than 3 million video frames of facial expressions, more than 1 thousand hours of accelerometer data, and approximately 1,400 hours of physiological data. Based on these preliminary data, they have achieved successful facial "Action Unit" detection for approximately 70 percent of video frames. Facial expression and activity and body position recognition require that the technology identify the individual patient as well as their real-time facial or bodily characteristics—a demanding technical task. Ongoing efforts include fine tuning of deep learning models using data collected from intensive care units (e.g., refining models for intubated patients), incorporating accelerometer and electromyography data to help recognize functional and pain-related activities such as restlessness and guarding, and developing real-time models to aid continuous in-hospital monitoring of critically ill patients. Ultimately, this technology will not replace nurses and physicians, but it will substantially augment their workflows and improve and standardize patient pain characterization.

Questions

Dr. Rashidi expects that this technology can be generalized to settings outside of the intensive care unit, although the deep learning models her team develops are specifically designed to work in that environment. In addition to pain, the AI system may also be leveraged to identify delirium by analyzing facial expressions or agitation by analyzing head poses, along with many other potential applications. In all cases, there is a tradeoff between using more sensors to generate more data, and appropriately limiting the data so that it is tractable for AI analysis.

Cell Type-Specific Midbrain and Extended Amygdala Contributions to Sex Differences in Pain and Drug Use

Waylin Yu, University of North Carolina at Chapel Hill

Although sex differences in pain sensitivity and perception are well-established, a meta-analysis of preclinical literature published between 1996 and 2006 found that 79 percent of papers used male subjects only. There is thus an unmet need to conduct more research on sex differences in pain sensitivity and prevalence, as well as in physiological responses to pain, and in how these factors influence the relationship between pain and drugs of abuse such as alcohol and opioids. For example, although males are more likely to use drugs of abuse to relieve pain symptoms, females are more vulnerable to developing chronic pain following a repeated drug exposure. Dr. Yu and colleagues have focused their research on two brain loci that they hypothesize are important for pain-drug interactions: (1) the periaqueductal grey (PAG), which gets activated

for threat response and drug-induced anti-nociception, and (2) the bed nucleus of the stria terminalis (BNST), which is a critical site for aversive states and pathological drug use.

Dr. Yu and colleagues explored whether dopaminergic neuron activity in the ventrolateral column of the PAG could alter pain sensitivity in both sexes through projections to the dorsal BNST. In an optogenetic approach, they expressed either channelrhodopsin 2 (ChR2) or a control virus in the PAG of male and female tyrosine hydroxylase-Cre mice and subsequently implanted an optic fiber over the dorsal BNST, allowing them to transfer light directly to the terminals of the PAG dopamine neurons in the BNST and control excitatory transmission between the two brain structures. They then combined this approach with Hargreaves and Von Frey tests to assess thermal and mechanical nociception during naïve pain states. Dr. Yu's team used the model to test sensitivity in an inflammatory pain model and see whether activation of the PAG dopamine projection could mitigate an inflammatory pain state. Assessing both sexes, the investigators found that the ChR2-expressing mice exhibit greater paw withdrawal latency, suggesting that the dopaminergic pathway can indeed reduce thermal nociception. However, this effect appeared to be much stronger in male mice. Von Frey data exhibited a similar pattern of greater mechanical sensitivity thresholds in ChR2-expressing male mice during naïve and inflammatory pain states, but not in females. Investigators have sought to identify a mechanism to explain this sexually dimorphic phenotype. Along the PAG-to-BNST dopamine circuit, they compared fast onset, high peak excitatory postsynaptic currents and slow onset, low peak inhibitory postsynaptic currents between males and females and found that females exhibit fewer polysynaptic connections than males yet exhibit similar monosynaptic connections. They also found that, along the PAG-to-BNST circuit, males release more dopamine, and that postsynaptic dopamine transmission along the circuit also differs between sexes. Current work to extend these findings includes recording the postsynaptic effects of dopamine transmission and determining the relationship of monosynaptic and polysynaptic connections with distribution of dopamine receptors D1 and D2 in both sexes.

Questions

Dr. Yu and colleagues have in situ data indicating an interplay between the anatomical locations of dopamine neuron terminals from PAG to BNST and how they are innervated by D2-receptor-positive fibers. However, those data have thus far focused only on the canonical BNST slice and have ignored related yet more extended regions, such as those reaching toward the striatum. Further work will be required to determine the relationship between distribution of D1 and D2 receptors and monosynaptic versus polysynaptic connections between sexes in the PAG-to-BNST projections.

Panel Session: Mid-Life Pain and Special Populations

Moderator: Cheryse Sankar, PhD, National Institute of Neurological Disorders and Stroke

Pain Prevalence in Vulnerable Populations

Richard L. Nahin, PhD, MPH, National Center for Complementary and Integrative Health

The Institute of Medicine (IOM) published a major report titled *Relieving Pain in America* (2011) which called for better national data "to describe the nature and extent of the [pain] problem" and "to identify subpopulations that will benefit more from future interventions." The IOM also stated that "there have been no systematic national studies of rates of undertreatment among [vulnerable populations]." Vulnerable populations are characterized by factors that increase the risk of pain or pain undertreatment or both, such as being older age or having lower education or income levels. Studying group differences in pain prevalence and treatment can provide insights into barriers thwarting appropriate care, especially for any groups disproportionately affected by or undertreated for pain. Here, "appropriate care" refers to care that follows evidence-based best practice guidelines. Dr. Nahin and collaborators published a study in the *Journal of Pain* (2019) leveraging data from the Medical Expenditure Panel Survey (MEPS), an annual, in-person, nationally representative household survey that tracks condition-specific health care use, including visits, procedures, tests, drugs, and other products. MEPS is administered by the Agency for Healthcare Research and Quality, which contacts providers to corroborate respondents' health care use.

MEPS data showing the age-adjusted annual prevalence of painful health conditions indicates the steepest increase in pain prevalence among adults aged 65 and older compared to younger adult cohorts from the years 1997/98 to 2013/14. Similarly, age-adjusted data representing the prevalence of any painful health condition by poverty status across those same two timepoints indicates that, in general, a negative correlation exists between an individual's socioeconomic status and likelihood of experiencing a pain condition (i.e., the lower the status, the higher the risk of pain). Age-adjusted education statistics are slightly more mixed, with individuals who have less than a high school education showing a milder increase in their pain prevalence than those with a high school degree. Moreover, those with a college degree have experienced a sharp rise in pain prevalence from 1997/98 to 2013/14, and as of 2013/14 had a higher overall pain prevalence than those with only a high school degree. MEPS data also show that poor and lower income individuals tend to visit the emergency room for pain treatment, while middle- and upper-income individuals tend to visit ambulatory clinics. In addition, those with less education attainment used more prescriptions for pain management than those with more education. Individuals with a high school degree or less increased their prescription opioid consumption significantly from 1997/98 to 2013/14—with the least educated experiencing the sharpest increase—while individuals with a college degree showed no statistically significant increase. Similarly, during the same time period, income level was negatively correlated with rising rates of strong opioid use for pain management. Investigators are currently analyzing these statistics in terms of more specific pain types and exploring variations by pain chronicity and severity, as well as by types and numbers of providers seen.

The NIH HEAL Initiative: Update

Francis Collins, MD, Director, National Institutes of Health

The United States is undergoing a joint crisis of pain and addiction. An estimated 50 million American adults are affected by chronic pain, with 25 million reporting severe daily pain and 20 million reporting high-impact chronic pain (i.e., pain that has persisted for at least 3 months and that restricts at least one major activity, such as attending school or performing housework). Also, more than 2 million Americans are addicted to opioids, and most such addictions began with legitimate prescriptions. During 2017, more than 70,000 Americans died of opioid overdoses, which constitutes a 9.6 percent increase from 2016. Although scientific research is improving understanding of addiction and pain, rapid translation of new knowledge into non-addictive approaches to pain management is urgently needed. To respond to this need, NIH has launched the HEAL (Helping to End Addiction Long-term) Initiative, which was introduced to the members of the pain consortium by Dr. Collins during last year's symposium. Dr. Collins provided an update, at a time when many pain and addiction researchers are increasing efforts to spend their allocated research funds in a coordinated and efficient manner to better understand and treat chronic pain and addiction. HEAL is a trans-NIH research effort to both (1) *enhance pain management,* and (2) *improve prevention and treatment strategies for opioid misuse and addiction*. HEAL receives $500 million per year, involves 12 NIH Institutes and Centers, and has released more than 40 funding announcements for fiscal year 2019. Because of delays in funds during its first year, HEAL can spend the leftover funds from the first year and thus has up to $850 million available during fiscal year 2019.

To enhance pain management, HEAL programs distinguish between preclinical and clinical research efforts. For example, one major preclinical aim is to develop a preclinical screening platform for pain that will leverage animal models of various human pain conditions. These models will allow investigators to efficiently evaluate candidate therapeutics in a preclinical setting, thereby accelerating execution of clinical trials to help displace opioids. This is paired with a major clinical initiative to construct an Early Phase Pain Investigation Clinical Network (EPPIC-Net) that will provide a prebuilt infrastructure for conducting Phase II clinical trials on private-sector compounds and devices that could provide feasible alternatives to opioids for pain management. Through a partnership with industry, up to 60 compounds have already been identified that never reached Phase II trials —not for lack of effectiveness—and that now receive an opportunity to enter clinical development. Other efforts aimed at testing novel treatments include the Back Pain Research Consortium (BACPAC), which includes basic science as well as translational and clinical efforts to understand mechanisms, develop new treatments, and optimize treatment use in the real world through better algorithms. In addition, the Pain Management Effectiveness Research Network (Pain-ERN) and Pragmatic and Implementation Studies for the Management of Pain (PRISM) aim to establish best strategies for management of acute and chronic pain.

Regarding HEAL's second overall aim to improve prevention and treatment of opioid misuse and addiction, NIH has launched various HEAL programs to (1) expand therapeutic options, (2) develop new and improved prevention and treatment strategies, (3) optimize effective

treatments, and (4) enhance treatments for newborns affected by maternal opioid exposure. As an example of these activities, Dr. Collins highlighted the need for evidence-based medicine to inform optimal duration of treatment recommendations. Currently, physicians have no evidence-based guidelines to determine when it is safe to stop treatment during remission.

In summary, HEAL Initiative research programs span the entire research cycle, from basic discovery, preclinical development, and clinical trials, to the crucial translational step of real-world clinical implementation and dissemination. Dr. Collins expects very intensive and continuous interactions between the HEAL initiative and the pain consortium in the coming years.

Pain and Pregnancy and the Postpartum

Brian Bateman, MD, MSc, Harvard University

Many types of pain are common during pregnancy, including low back pain, pelvic girdle pain, hip and knee pain, and leg cramps. These often coexist with acute and chronic pain conditions that predate the pregnancy. Dr. Bateman and colleagues studied a cohort of more than 500,000 pregnant women and found that 14.4 percent of them had used opioids at some point during pregnancy. Moreover, Dr. Rishi Desai and colleagues have documented increased prescription opioid use during pregnancy among Medicaid-enrolled women; specifically, 21.6 percent filled a prescription and 3 percent received greater than a 30-day supply of opioids during pregnancy. Opioid use among pregnant women in the United States far exceeds rates in other developed Western countries such as Canada, Norway, and Scotland. Exposure to prescription opioid analgesics in utero can increase the risk of neonatal abstinence syndrome. This risk increases with the dose and duration of exposure; exposure during late pregnancy also heightens risk. Endogenous opioids help to regulate fetal development, and exogenous opioids may adversely impact this process. Animal studies suggest that opioids may be toxic to the developing cardiac system and CNS. Other potential risks from fetal opioid exposure include placental abruption, stillbirth, preterm delivery, and intrauterine growth restriction. However, the studies evaluating such risks suffer from multiple sources of bias (e.g., recall and confounding bias), small sample sizes, and scant data on specific opioids, timing, or dose. Better studies are needed, as are more nonpharmacologic treatments that are tailored specifically to pain during pregnancy.

Postpartum pain is also common, particularly following cesarean delivery (CD), which accounts for approximately 30 percent of all deliveries and is the most common inpatient surgery in the United States. Opioids are routinely prescribed in the United States following CD, and over-prescription is common. Medical opioid use for acute indications following CD can transition into chronic, nonmedical opioid use, which can develop into an addiction to dangerous substances such as heroin. Initial prescriptions of opioids following CD often constitute a critical initial exposure for opioid-naïve women who may then develop persistent use habits. Risk factors for persistent opioid use post CD among opioid-naïve women include younger age, smoking, cocaine abuse, pain conditions, antidepressant use, and benzodiazepine use. Excessive prescribing often also leads to leftover medication that is then available for abuse, helping to fuel the opioid crisis. One study found that approximately 70 percent of those who

use opioids nonmedically obtain them from a friend or family member, highlighting a need to define normative opioid requirements to avoid overprescribing. Extrapolating results from study published in *Obstetrics and Gynecology* (2017), it seems that approximately 20 million opioid tablets enter communities each year as leftover medication after treatment of pain following CD. This highlights the urgent need to better align prescriptions with actual medical need. Relevant research gaps include the need to develop and evaluate strategies to prevent transition to chronic use/misuse and to refine comparative strategies for postpartum analgesia in patients with opioid use disorder.

Chronic Pain in People with Long-Term Disability—What Do We Know, and What Do We Need?

Ivan R. Molton, PhD, University of Washington

Much research on pain in aging focuses on formerly able-bodied adults who are aging "into" a new disability. However, a growing literature focuses on individuals who are aging "with" long-term physical disability (LTPD) due to early-acquired conditions such as multiple sclerosis, spina bifida, cerebral palsy, and spinal cord injury. Such conditions vary regarding onset, progression, and trajectory across the lifespan. Among those with LTPD, chronic pain is the norm, and it is associated with activity restriction and avoidance, sleep disruption, depression and anxiety, decreased social participation, and higher medical services utilization and cost. Most people with pain related to LTPD report multiple pain locations, types, and severities. "Primary pain" refers to pain that is caused by the underlying pathology of the disease itself, in contrast to "secondary pain," which refers to pain that indirectly results from the disease (e.g., shoulder osteoarthritis caused by years of operating a wheelchair). In people with LTPD, chronic pain is inseparably linked with fatigue (i.e., activity restrictions due to fatigue contributes to further pain related problems) and can limit mobility and social participation in specific ways, such as avoiding trips via public transportation due to the associated pain. Another key relationship among people with LTPD is that between fear of pain and fear of falling. Falling is common among people with LTPD, and fear of falling is associated with gait abnormalities, such as slow and short walking steps. Within this population, chronic pain is also frequently associated with involuntary early retirement, which affects financial trajectories. Approximately 39 percent of individuals with LTPD retire involuntarily.

Access to medical care is also more limited among individuals with LTPD. Barriers to accessing rehabilitation specialists include health insurance restrictions, lack of nearby specialists, and lack of transportation options. In one study, approximately 20 percent of people with LTPD skipped or delayed care due to transportation barriers or an inability to cover out-of-pocket expenses. Overall, middle age is the period of greatest vulnerability for people with LTPD. This period is associated with the highest levels of pain severity and interference, the highest rates of reported falls and depression, and the lowest-rated happiness and quality of life. Some common psychosocial stressors during midlife in people with LTPD include marriage, change of residence or career, and retirement. Moreover, health-related changes themselves constitute important midlife stressors for individuals with LTPD, such as worsening of pain or fatigue and change in function or dismissal from work. While some studies have shown that pain severity

increases with age and that pain interference decreases post-retirement, this is not true for people with LTPD. For these individuals, pain interference remains stable throughout older adulthood. Pain in people with LTPD exists in a complex network of social relations, and treatment requires biopsychosocial approaches. Given that people with LTPD continue to face stigmatization and discrimination in many aspects of their lives, pain management for this population could be thought of as a civil rights issue. Gains in access and inclusion are often hard-fought, and the current dialogue surrounding opioids for pain must be understood against the historical backdrop of the unique challenges faced by people with LTPD.

Panel Session Q&A

MEPS Data and Opioid Prescription Guidelines
MEPS collects data annually, although data from each collection wave take 2 years until they are released. One participant noted the potential value of MEPS data in observing shifts in opioid prescribing practices around 2014 due to the release of various opioid prescription guidelines, such as that by the Centers for Disease Control and Prevention (CDC).

Potential Hazards of Health Care Access
Easy access to health care providers can sometimes elevate one's risk of acquiring an opioid addiction. For example, overprescribing of opioids and the resulting misuse of leftover drugs is most likely to affect those with ready access to prescribing physicians. Moreover, even people with medical training are vulnerable to overusing opioids when provided excessive allotments.

Postpartum Psychosocial Stress
Particularly for women who undergo CD, the postpartum period is often characterized by stress and emotional turbulence. To help reduce the prevalence of opioid use and misuse among that population, providers must work to develop nonpharmacologic or biopsychosocial approaches to both stress and pain management.

Cohort Effects in Midlife Data
Sir Deaton hypothesized that the dip in midlife satisfaction that Dr. Molton presented might be caused by an unidentified cohort effect. Dr. Molton and his colleagues have not ruled out that possibility.

Mitchell Max Award Presentation

Ann K. Cashion, PhD, RN, FAAN; Acting Director, National Institute of Nursing Research

The 2019 Mitchell Max Award was presented to Dr. Michael Burton for his presentation titled "Delayed Onset of Neuropathic Pain in Aged Males After Peripheral Nerve Injury." Dr. Burton earned a BS and a PhD in animal sciences with a focus on immunophysiology and behavior at the University of Illinois at Urbana-Champaign and is now an Assistant Professor of Systems Neuroscience at the University of Texas at Dallas.

Day 2 Meeting Summary

Introduction to Day 2

Martha Somerman, DDS, PhD, Director, National Institute of Dental and Craniofacial Research

Approximately 7 percent of the National Institute of Dental and Craniofacial Research (NIDCR) budget is dedicated to addressing orofacial pain. NIDCR research on pain includes the study of pain caused by dental surgery, oral cancer, Burning Mouth Syndrome, and other conditions such as temporomandibular joint disorders. Dr. Jerome Adams, Surgeon General of the U.S., has indicated that he is passionate about oral health and has commissioned a 2020 Surgeon General's Report on Oral Health in America. Opioids, which are another high priority of the Surgeon General, will be a major focus of the report. One section of the report will address the "effects of addiction and mental health disorders on oral health." An important topic area within this section will cover orofacial pain, pain management, and opioid misuse. Opioids may be prescribed to treat acute pain after dental procedures or orofacial surgery. It is estimated that more than half of 14- to 17-year-olds receive opioid prescriptions from dentists following wisdom tooth extractions. In 2010, dentists were the third most frequent prescribers of opioids. Due to increased awareness in recent years, they are now only the fifth most frequent prescribers. NIDCR is investing in developing nonopioid treatments, implementing and disseminating alternative pain management strategies, and working across NIH and other federal agencies (e.g., through the HEAL Initiative and Pain Committees). It also establishes training programs and partnerships with dentists and dentistry organizations, such as the American Dental Association (ADA) and the American Dental Education Association.

The Role a Professional Association Can Play in Stemming the Opioid Crisis—Acute Pain Management and Policy Changes

Jeffrey M. Cole, DDS, President, American Dental Association

The mission of the ADA is to support all of its members, especially when they are struggling with personal and professional difficulties, including addiction. Mental health afflictions and psychosocial pressures, emotional distress, and increased access to opioids all contribute to producing an environment that puts people, including professional health care providers, at heightened risk for substance abuse and the resulting dangers to health. When supporting or caring for those experiencing addiction (e.g., as a result of opioid prescribing for pain management), it is vital to understand, on a personal level, the impact that substance use disorders can have both on ADA members and on patients, and to respond with compassion. ADA's policy on opioid prescribing supports (1) mandatory continuing education in prescribing opioids and other controlled substances, (2) statutory limits on opioid dosage and duration of no more than 7 days for the initial treatment of acute pain—consistent with the CDC evidence-based guidelines—and (3) registration and utilization, among dentists, of prescription drug monitoring programs to promote appropriate use of opioids.

A Patient's Perspective

Caregiving and the Future of Pain Management: Where Do We Go from Here?

Jasmine Pearlman, MPA, Host & Executive Producer, "Caregiving & You"

Ms. Pearlman became her mother's primary caregiver when she was diagnosed with non-Hodgkin's lymphoma. Her mother was frightened and angry about her diagnosis but achieved remission after 2 years. However, after another 2 years, she had developed chronic pain and required further care by Ms. Pearlman. As family caregiver, particularly during her mother's long bout with chronic pain, Ms. Pearlman adopted diverse responsibilities to help support her mother and facilitate her care and recovery. For example, she not only managed her mother's pharmaceutical supply and regimen, but also became responsible for managing her recreational activities. Such diverse roles and responsibilities commonly rest with primary family caregivers.

Ms. Pearlman's mother suffered from nine chronic pain conditions simultaneously—including rheumatoid arthritis, fibromyalgia, osteoarthritis, and glaucoma— and thus required very time-consuming care. While caring for her mother, Ms. Pearlman confronted a wide range of challenges that she shared with symposium participants, including (1) getting organized, (2) comforting her mother to alleviate her suffering, (3) fostering effective emotional intelligence and communication skills to facilitate her mother's care, (4) distinguishing different levels and types of pain to help gauge appropriate care approaches on a day-to-day basis, (5) developing complementary medicine plans that included nonpharmacologic therapies such as yoga, massage, and meditation, (6) building alliances among patient, caregiver, and providers (7) obtaining pain relief from drugs while avoiding complicating and dangerous side effects, (8) acquiring opioids when necessary despite "opioid paranoia," and (9) caring for herself while focusing on caring for her mother.

Leveraging her experience, Ms. Pearlman offered the following practical advice for family caregivers: (a) make a complete inventory of your loved one's physical, emotional, spiritual, economic, and social challenges to be addressed, (b) create a clear plan of action based on patient involvement to address these challenges, and (c) provide a comfortable "pain friendly" home. She also advised patients to (a) prepare for opioids becoming unavailable, (b) realize that chronic pain could become your "new normal," (c) cooperate fully with family caregivers and health care providers, and (d) find enjoyable, meaningful outside activities.

Panel Session: Pain Management in Older Adults

Moderator: Basil Eldadah, MD, PhD, National Institute on Aging

Overview: Pain Management in Late-Life

Keela Herr, PhD, RN, AGSSF, FGSA, FAAN, University of Iowa

Unique Challenges of Pain in Late Life

As the demography of the U.S. population shifts—with aging baby boomers—toward a higher proportion of elderly people, overall prevalence of pain is correspondingly increasing. Estimates

are that approximately 20 percent of the population will be older than 65 by the year 2020. The increased prevalence of untreated pain in older age is closely related to increased prevalence of a variety of comorbidities such as sleep disturbance, social isolation, falls or declining mobility and physical function. It is also linked to declining mental health, which manifests in symptoms such as anxiety, depression, impaired cognition, and suicidal ideation. Untreated chronic pain and its associated diverse comorbidities lead eventually to increased health care use and cost. Moreover, unique combinations of risk factors challenge chronic pain management for older adults, including the physiological and cognitive changes that accompany aging, as well as multidrug regimens that are commonly used by the elderly, which introduce complications such as drug-drug interactions and compliance issues. Healthcare providers are often inadequately trained in pain care for geriatric patients, which leads to improper balancing of benefits and risks when constructing individualized treatment plans. These challenges affect both the recognition and evaluation of pain and treatment of pain in older adults. Pain assessment in older adults should involve, in addition to physical examinations, self-reports, behavioral observations, and evaluation of psychosocial comorbidities and other complicating factors such as cognition and affect. Pain intensity scales such as the Iowa Pain Thermometer, the PEG Scale, as well as functional pain scales can also help with pain evaluation.

Pain and Dementia

One subpopulation of elderly adults whose pain conditions are especially difficult to evaluate are those with dementia. Pain patients with dementia often have trouble clearly or consistently communicating to providers the type and intensity of their pain experiences. The most stable (i.e., reliable and valid) available tool for assessing pain intensity in cognitively impaired older adults are the Verbal Rating Scales. Some research has also indicated a possibility for leveraging physiological measures such as fMRI or electroencephalography to measure pain in adults with dementia. Pain behavior observation might add value, although behavioral variability, difficulty establishing pain intensity, overlap of behaviors associated with other conditions, and lack of normative information to help interpret behavioral scores hinder integration of pain behavior measures in such assessments. Nevertheless, observation of body movements such as restlessness (indicating agitation), rubbing, guarding, rigidity, and physical aggression has demonstrated value in assessing pain. Facial grimace constitutes another possible behavioral indicator of pain. Investigators are developing a pain identification and communication toolkit for family caregivers of persons with dementia.

Treating Pain Among the Elderly

Treatment of pain in older adults—with the goal of achieving optimal pain relief—requires a balanced consideration of the risks and benefits associated with various treatment approaches. Recent guidelines and standards, such as those released by CDC and by the U.S. Department of Veteran's Affairs, encourage nonpharmacologic—and specifically nonopioid—approaches for pain treatment. Such approaches include physical treatments such as exercise, massage, and acupuncture or assistive devices, as well as cognitive-behavioral treatments such as cognitive and behavioral therapies, mindfulness meditation, distraction, and self-management programs. Evidence supporting such treatments indicates small-to-moderate effects on pain and function, however, and long-term effectiveness remains poorly defined. Randomized controlled trials of

pharmacologic treatments, however, also show small-to-moderate effects for pain relief, and studies exploring pain in older patients with comorbidities, including dementia, are limited, as are studies leveraging racially diverse samples or multimodal treatments. Key priorities for future research include refining assessment approaches and evaluating effectiveness of interventions in real-world settings.

Pain in Nursing Home Residents

Kate Lapane, PhD, MPH, University of Massachusetts

As the proportion of elderly Americans increases, so does the need for caregivers. Among individuals living in nursing homes, 40 to 60 percent experience pain, and approximately 20 percent have persistent pain. However, pain management in nursing homes is severely lacking, despite becoming an increasingly essential setting for provision of care for cancer patients and others with complex health needs. The Minimum Data Set (MDS), which was authorized by U.S. Congressional mandate, provides clinical assessment data on all residents of nursing homes that are Medicare or Medicaid certified. A study by Dr. Christine Ulbricht and colleagues used MDS data to group nursing home residents into four pain subgroups: (1) severe (15.2 percent), (2) moderate, frequent (26.4 percent), (3) moderate, occasional with depressive symptoms (26.4 percent), and (4) moderate, occasional without depressive symptoms (32.0 percent). Several barriers hinder the ability of nursing home staff to recognize pain in residents, including residents regarding pain as a normal part of aging (and therefore not reporting it), and concern among residents about not being "good patients." In addition, many providers are inadequately trained to recognize pain conditions in elderly people, especially those with dementia, which is exacerbated by a lack of standardized pain assessment instruments.

Improving pain in nursing homes requires valid and reliable methods of recognizing, assessing, and treating a wide variety of pain conditions, especially by nonpharmacologic approaches. Providers should, in general, seek to optimize and preserve patient functionality and quality of life, while recognizing that practical treatment goals necessarily differ among patients. For bed-bound residents, sleep hygiene and appetite are especially important features to monitor, because disturbances in these can indicate that a resident is experiencing pain. For others, gait speed and interaction with other residents can be similarly indicative. The publication *Pain Management for Older Adults* (2009) contained a set of guidelines, recommending opioids to manage moderate to severe nonmalignant pain, especially if it affects function or diminishes quality of life. CDC released its *Guideline for Prescribing Opioids for Chronic Pain* (2016), which listed risk factors for opioid-related adverse events such as overdose. However, CDC guidelines largely focus on younger adults, and much remains unknown about the prevalence of CDC's listed risk factors among nursing home residents. Nevertheless, a recent study by Dr. Ulbricht and colleagues (2018) suggests that a substantial proportion of nursing home residents receive opioid prescriptions, with long-term users receiving long-acting opioids and high average daily doses. Another publication by Dr. Jacob Hunnicutt and colleagues (2018) revealed that opioid consumption among nursing home residents varies dramatically by state. There is an unmet need to characterize pain subgroups among nursing home residents. Improving the evidence base for this largely neglected population should be a research priority.

Cognition and Sleep in Older Adults with Chronic Pain—Symptoms or Mechanisms for Change?

Christina McCrae, PhD, University of Missouri-Columbia

Although investigators have known that cognition and sleep are in some ways related to pain, the nature of these relationships has been elusive. Up to 31 percent of older adults self-report chronic pain, and between 50 and 88 percent of chronic pain patients report sleep disturbances. Up to 50 percent of older adults report chronic insomnia, half of whom also report chronic pain. Studies among older adults also consistently find that chronic pain is associated with a variety of cognitive deficits, including reduced performance in working memory, immediate memory, language, delayed memory, and mental flexibility. In addition, some mixed evidence suggests that in older adults, chronic insomnia and cognitive deficits may be related. For example, poor sleep quality has been associated with worse performance on executive function tests, yet not on episodic memory or processing speed assessments, and longer total wake time has been found to be associated with better performance on a sustained attention and processing speed task. Investigators have also conducted studies among older adults that revealed no relationship between insomnia and cognition, yielding a mixed and uneven evidence base.

To address these ambiguities, Dr. McCrae and colleagues have conducted four studies exploring relationships among insomnia, pain, and cognition. The first study assessed cognition of older adults with chronic insomnia who either did or did not have a chronic pain history. They found that insomnia was most strongly associated with poor cognitive performance among older adults with a history of chronic pain. Their second study examined sleep quality among middle-aged adults who suffer from chronic widespread pain and its interaction with cognitive performance, finding that, within the high-pain-intensity group, cognitive assessment scores were substantially worse among individuals with low sleep quality compared to those with average or high sleep quality. A third study, of older adults with implantable cardioverter defibrillators who experienced insomnia and a range of pain symptoms, explored relationships between “sleep efficiency” and ventricular arrhythmias. It also investigated interactions of these symptoms with pain ratings and cognitive performance. Among the “high pain” group, significant differences emerged among those with low, average, and high sleep efficiency: greater sleep efficiency was associated with better cognitive performance. A fourth study examined sleep efficiency and its interaction with pain ratings on cognitive performance among sedentary older adults with a range of sleep and pain phenotypes. The data indicate a significant relationship between poor sleep efficiency and poor cognitive performance.

Taken together, the results of these studies strongly suggest that worse pain, worse sleep, and worse cognitive performance are all closely related. Specifically, results suggest that for those with a history of chronic pain, worse sleep is associated with worse lower-order functioning, while for those without a history of chronic pain, worse pain ratings are associated with worse attention, processing speed, and verbal memory. Across all studies, better sleep was associated with better cognitive performance at higher levels of pain. However, these studies all have

limitations (e.g., small sample sizes, limited generalizability) and further research is needed, particularly to focus on mechanisms for behavioral or cognitive interventions.

Biological Aging Biomarkers as Outcome Measures of Pain in Older Adults

Yenisel Cruz-Almeida, MSPH, PhD, University of Florida

Dr. Cruz-Almeida's laboratory studies the relationships between pain and aging, specifically investigating whether pain might accelerate aging processes. At the core of this work is the recognition that aging is more complex than the simple concept of chronological age suggests. Some of the underlying complexities (e.g., differences in aging patterns at the organ versus cellular levels) can be leveraged to interrogate the complex relations between pain and aging. Aging can generally be defined as a gradual accumulation of deleterious biological changes and progressive loss of function that increases the risk of morbidity and mortality; however, all of these features exhibit significant individual-level variability. Pain, correspondingly, has been defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." However, pain is in fact a complex, multidimensional experience that involves unique combinations of emotional-affective, cognitive-evaluative, and sensorimotor components. Acute pain, in particular, is necessary for survival and depends upon many brain regions to produce an integrated experience of pain recognition, evaluation, and response.

The diverse brain regions involved in pain experience, and the evident relationships between pain and aging, have led Dr. Cruz-Almeida and colleagues to investigate whether brain aging might play a direct role in amplifying pain experiences. They have leveraged multimodal imaging techniques to study neuromodulation of pain and mobility over the lifespan. Study participants were cognitively healthy older adults who were eligible for MRI, could walk unassisted, had zero exposure to opioids and were in overall good health. Investigators hypothesized that individuals with chronic pain would have "older" brains for their age compared to those without chronic pain. They quantified brain aging using Dr. James Cole and colleagues' (2017) machine learning algorithm, which models trajectories of healthy brain aging, providing a "brain age" that may differ from one's chronological age. By comparing an individual's predicted brain age to their biological age, investigators can compare brain aging across groups. A "younger" brain age is associated with years of education and amounts of physical exercise and mediation practice. An "older" brain age is associated with various negative health outcomes, including Alzheimer's disease, schizophrenia, poor lung function, and overall mortality risk.

Older participants who did not report experiencing chronic pain within the past 3 months had significantly younger brains than participants who did. On average, the brains of participants in the latter group were approximately 2 years older—each relative to their own biological ages—than in the former group. Moreover, the higher the pain intensity, the older the measured brain age. Older brain age was also positively correlated with *untreated* pain (as gauged by asking participants whether they had received any pain treatment within the past 3 months). Those who reported pain but also received pain treatment exhibited brain ages as young as

participants who reported having no chronic pain at all. Younger brains were also associated with better somatosensory function, more efficient endogenous pain modulation, and higher positive affect, agreeableness, and emotional stability. Dr. Cruz-Almeida and colleagues have also leveraged an epigenetic aging biomarker to obtain results reflecting similar overall patterns—in the same sample—to those found using the brain age biomarker.

Panel Session Q&A

Variety in Drugs and in Dosage

Dr. Lapane's data indicated widespread heterogeneity in the drugs prescribed to treat pain in nursing homes across the United States, specifically at the state level, suggesting that this heterogeneity is a result of variation in states' prescription regulations. One participant emphasized that each of the drugs with presented data (i.e., oxycodone, hydrocodone, and tramadol) is associated with different side effects at different doses, suggesting a potential need to investigate how the differences in drugs and dosages across these states may vary systematically. Dr. Lapane agreed and emphasized that these data have been corrected for dose effects.

Different Pain Types and Their Impact on Self-Care Behaviors

Many of the pain treatments that Dr. Cruz-Almeida's participants reported receiving during the 3 months prior to the study appeared to involve self-care. The impacts of specific types of pain on self-care behavior could potentially be a fruitful area for future research, as some pain types disproportionately affect cognitive functions such as motivation and goal-oriented behavior, which may in turn influence one's tendency or ability to administer self-care.

Epigenetics, Telomere Length, and Brain Aging

Dr. Cruz-Almeida and colleagues have submitted a grant proposal that suggests using biosamples from the research participants to investigate the relationships among brain aging and other biomarkers such as telomere length and those derived from epigenetics.

Pain Management Best Practices Inter-Agency Task Force

Alicia Richmond Scott, MSW; Designated Federal Officer, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services

The U.S. Departments of Health a Human Services, Defense, and Veteran's Affairs oversee the Pain Management Best Practices Inter-Agency Task Force ("the Task Force"), initially authorized by the Comprehensive Care and Recovery Act of 2016. The Task Force issues recommendations and updates best practices regarding management of acute and chronic pain, with an emphasis on individualized, multimodal, and multidisciplinary approaches. Since its authorization, the Task Force has drafted, opened for public comment, and finalized and published its *Report on Pain Management Best Practices: Updates, Gaps, Inconsistencies, and Recommendations*. The report contains five main sections: (1) Medications, (2) Restorative Therapies, (3) Interventional Procedures, (4) Behavioral Health Approaches, and (5) Complementary and Integrative Health. Four themes cut across all of these sections: (a) risk assessment, (b) stigma, (c) access to care,

and (d) education. The Task Force concluded that these four themes are each critically important in acute and chronic pain management across all treatment modalities.

The Task Force's report also updated recommendations for best practices by integrating innovative solutions to pain management such as telemedicine, telemonitoring, and mobile apps into its suggested framework, in part to overcome barriers to broader implementation of behavioral health approaches to pain management. The report also highlights the pain management needs of various special populations, such as children, women, older adults, American Indians/Alaskan Natives, active duty soldiers and veterans, and sickle-cell disease patients. Further research is required to develop a better understanding of pain mechanisms and preventive measures, as well as of how best to leverage innovative medical devices and medications for pain relief.

Closing Remarks

Nora Volkow, MD, Director, National Institute on Drug Abuse

The double-crisis of pain and opioids that the United States is currently experiencing affects Americans at all stages of life. More research is urgently needed to fight overprescribing and misuse/abuse of opioids, and to improve pain management by developing viable opioid alternatives. During the symposium, one participant noted that the volume of research needed to address these issues introduces challenging recruitment needs. In response, Dr. Volkow highlighted the potential to leverage large-scale NIH studies such as All of Us as recruitment pools for pain-related research. The NIH HEAL and BRAIN (Brain Research through Advancing Innovative Neurotechnologies) initiatives represent further research opportunities. Pain is a necessary and inevitable aspect of life, yet it is often pathological—particularly chronic pain. This symposium, and the entire NIH Pain Consortium, are testaments to the unmet needs in pain management, but also to the opportunities to advance knowledge in the pain research field.

Appendix A

14th Annual NIH Pain Consortium Symposium on Advances in Pain Research

Pain Across the Lifespan

May 30 - 31, 2019

Masur Auditorium and FAES Terrace, NIH Clinical Center, NIH Main Campus

May 30, 2019	
8:30 am	**Welcome and Opening Remarks** Helene Langevin, M.D., Director, National Center for Complementary and Integrative Health
8:45 am	**Keynote Address: Pain and Opioids in an Epidemic of Mental and Economic Distress** Sir Angus Deaton, Ph.D. & Anne Case Ph.D., Princeton University
9:45 am	**Break and Poster Session *(FAES Terrace)***
10:15 am	**Panel Session: Pain in Pediatric Populations** **Moderator:** James A. Griffin, Ph.D., National Institute of Child Health and Human Development ***Overview: Biopsychosocial Predictors of the Transition from Acute to Chronic Pain in Children and Adolescents*** Tonya Palermo, Ph.D., University of Washington
10:45 am	***Migraine in Youth: Building the Evidence Base and Discovering Mechanisms of Effective Treatment*** Scott Powers, Ph.D., ABPP, FAHS, Cincinnati Children's Hospital

11:05 am	***From Mechanisms to Intervention: Central Pain Processes in Primary Dysmenorrhea*** Laura Payne, Ph.D., University of California Los Angeles
11:25 am	***Studying the Transition from Acute to Chronic Pain After Traumatic Stress*** Samuel McLean, M.D., M.P.H., University of North Carolina at Chapel Hill
11:45 pm	***Panel Session Q&A***
12:05 pm	**Networking Lunch and Poster Session *(FAES Terrace)***
1:15 pm	**Introduction of Junior Investigator Presentations** Helene Langevin, M.D., Director, National Center for Complementary and Integrative Health
1:25 pm	***Delayed Onset of Neuropathic Pain in Aged Males After Peripheral Nerve Injury*** Michael D. Burton, Ph.D., University of Texas at Dallas
1:40 pm	***Autonomous Pain Recognition in Critically Ill Patients*** Parisa Rashidi, Ph.D., University of Florida
1:55 pm	***Cell Type-Specific Midbrain and Extended Amygdala Contributions to Sex Differences in Pain and Drug Use*** Waylin Yu, University of North Carolina at Chapel Hill
2:10 pm	**Panel Session: Mid-Life Pain & Special Populations** **Moderator:** Cheryse Sankar, Ph.D., National Institute of Neurological Disorders and Stroke ***Pain Prevalence in Vulnerable Populations*** Richard L. Nahin, Ph.D., M.P.H., National Center for Complementary and Integrative Health
2:40 pm	**The NIH HEAL Initiative: Update** Francis Collins, M.D., Director, National Institutes of Health
3:00 pm	**Break and Poster Session *(FAES Terrace)***
3:25 pm	***Pain and Pregnancy and the Postpartum*** Brian Bateman, M.D., M.Sc., Harvard University
3:45 pm	***Chronic Pain in People with Long-Term Disability—What do we Know, and What do we Need?*** Ivan R. Molton, Ph.D., University of Washington
4:05 pm	***Panel Session Q&A***

4:20 pm	**Mitchell Max Award Presentation** Ann K. Cashion, Ph.D., RN, FAAN, Acting Director, National Institute of Nursing Research
4:35 pm	**Adjourn**

May 31, 2019

8:30 am	**Introduction** Martha Somerman, D.D.S., Ph.D., Director, National Institute of Dental and Craniofacial Research **The Role a Professional Association Can Play in Stemming the Opioid Crisis—Acute Pain Management & Policy Changes** Jeffrey M. Cole, D.D.S., President, American Dental Association
8:55 am	**A Patient's Perspective** **Caregiving and the Future of Pain Management: Where Do We Go from Here?** Jasmine Pearlman, M.P.A, Caregiving & You, Host & Executive Producer
9:15 am	**Panel Session: Pain Management in Older Adults** **Moderator:** Basil Eldadah, M.D., Ph.D., National Institute on Aging ***Overview: Pain Management in Late-Life*** Keela Herr, Ph.D., RN, AGSF, FGSA, FAAN, University of Iowa
9:45 am	***Pain in Nursing Home Residents*** Kate Lapane, Ph.D., M.P.H., University of Massachusetts
10:05 am	**Break and Poster Session *(FAES Terrace)***
10:35 am	***Cognition and Sleep in Older Adults with Chronic Pain—Symptoms or Mechanisms for Change?*** Christina McCrae, Ph.D., University of Missouri-Columbia
10:55 am	***Biological Aging Biomarkers as Outcome Measures of Pain in Older Adults*** Yenisel Cruz-Almeida, MSPH, Ph.D., University of Florida
11:15 am	***Panel Session Q&A***
11:35 am	***HHS Pain Management Best Practices Inter-Agency Task Force*** Vanila M. Singh, M.D., MACM, Chief Medical Officer, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services
11:55 am	**Closing Remarks** Nora Volkow, M.D., Director, National Institute on Drug Abuse

12:15 pm	**Adjourn**

Appendix 2: Meeting Participants

Executive Committee

Walter Koroshetz), Director, National Institute of Neurological Disorders and Stroke
David Shurtleff, Director, National Center for Complementary and Integrative Health
Ann Cashion, Acting Director, National Institute of Nursing Research
Martha Somerman, Director, National Institute of Dental and Craniofacial Research
Nora Volkow, Director, National Institute on Drug Abuse
Staff: NINDS Office of Pain Policy: Linda Porter (Director)

Speakers and Moderators

Brian Bateman, M.D., M.Sc.
Harvard University

Anne Case, Ph.D.
Princeton University

Ann K. Cashion, Ph.D., RN, FAAN
National Institute of Nursing Research; NIH Pain Consortium Executive Committee

Jeffrey M. Cole, D.D.S.
President, American Dental Association

Francis Collins, M.D., Ph.D.
Director, National Institutes of Health

Yenisel Cruz-Almeida, MSPH, Ph.D.
University of Florida

Sir Angus Deaton, Ph.D.
Princeton University

Keela Herr, Ph.D., RN, AGSF, FGSA, FAAN
University of Iowa

Helene Langevin, M.D.
National Center for Complementary and Integrative Health

Kate Lapane, Ph.D., M.P.H.
University of Massachusetts

Christina McCrae, Ph.D.
University of Missouri-Columbia.

Samuel McLean, M.D., M.P.H.
University of North Carolina at Chapel Hill

Ivan R. Molton, Ph.D.
University of Washington

Richard L. Nahin, Ph.D., M.P.H.
National Center for Complementary and Integrative Health

Tonya Palermo, Ph.D.
University of Washington

Laura Payne, Ph.D.
University of California Los Angeles

Jasmine Pearlman, M.P.A.
Caregiving & You, Host & Executive Producer

Scott Powers, Ph.D., ABPP, FAHS
Cincinnati Children's Hospital

Alicia Richmond Scott, MSW
U.S. Department of Health and Human Services

Martha Somerman, D.D.S., Ph.D.
National Institute of Dental and Craniofacial Research; NIH Pain Consortium Executive Committee

Nora Volkow, M.D.
National Institute on Drug Abuse; NIH Pain Consortium Executive Committee

NIH Pain Consortium Members

National Cancer Institute
National Eye Institute
National Heart, Lung, and Blood Institute
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Biomedical Imaging and Bioengineering
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Disorders

National Institute of General Medical Sciences
National Institute of Mental Health
National Institute of Neurological Disorders and Stroke
National Institute of Nursing Research
National Institute on Aging
National Institute on Alcohol Abuse and Alcoholism
National Institute on Deafness and Other Communication Disorders
National Institute on Drug Abuse
National Institute on Minority Health and Health Disparities
John E. Fogarty International Center
National Center for Advancing Translational Sciences
National Center for Complementary and Integrative Health
Warren Grant Magnuson Clinical Center
Office of the Director

- Office of Behavioral and Social Sciences Research
- Office of Technology Transfer
- Office of Rare Diseases
- Office of Research on Women's Health