13th Annual NIH Pain Consortium Symposium on Advances in Pain Research

From Science to Society: At the Intersection of Chronic Pain Management and the Opioid Crisis

May 31 to June 1, 2018

Bethesda, Maryland

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Acronym Definitions

APS	American Pain Society
BRAIN	Brain Research through Advancing Innovative Neurotechnologies Initiative
Cdk5	cyclin-dependent kinase 5
CNS	central nervous system
CPM	Conditioned Pain Modulation
DREADD	designer receptor exclusively activated by designer drugs
GFP	green fluorescent protein
HEAL	Helping to End Addiction Long-term Initiative
KOR	kappa-opioid receptor
NIH	National Institutes of Health
PAG	periaqueductal gray
PET	positron emission tomography
PNS	peripheral nervous system
PTSD	posttraumatic stress disorder
SCC	squamous cell carcinoma
TRL4	toll-like receptor 4
VH	virtual human
VR	virtual reality
VTA	ventral tegmental area

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Introduction

The NIH Pain Consortium was created in 2003 to foster collaboration across National Institutes of Health (NIH) Institutes and Centers involved in pain research. The Consortium held its 13th Annual Symposium on May 31 and June 1, 2018, on the NIH Campus in Bethesda, Maryland. The Symposium offers researchers and health care providers a chance to convene and learn about recent advances in pain research, clarify priorities for ongoing efforts, and discuss opportunities to improve knowledge and treatment of pain.

This year's Symposium focused on the joint crisis of chronic pain management and opioid addiction. It featured a keynote address by Judith Paice, RN, PhD, who highlighted the unintended consequences of restricting opioid prescriptions for chronic pain patients. Indeed, the complicated interactions among the physiology, psychology, and demography of chronic pain and opioid abuse was a theme throughout the Symposium. The emphasis on these interactions encouraged participants to think creatively about how to reverse the crisis and highlighted the need to consider the unintended consequences of too narrowly focused solutions.

Francis Collins, PhD, NIH Director, presented the NIH HEAL (Helping to End Addiction Long-term) Initiative and hosted a Fireside Chat with U.S. Surgeon General, Vice Admiral Jerome Adams, MD, MPH. Their discussion, including a question and answer session, focused on translating research outcomes into health outcomes, recognizing that social stigma contributes to patient deaths, and achieving better health through better partnerships among academia, communities, public and private organizations, and industry.

The presentations and discussions approached pain management from a variety of perspectives, including interactions between pain and reward circuitry in opioid action, demographic disparities in pain management, a patient's perspective on the intersection of chronic pain and opioid restrictions, and non-opioid neurotechnologies developed under the NIH BRAIN Initiative. The Symposium also featured a series of presentations by junior investigators nominated for the annual Mitchell Max Award.

Day 1 Meeting Summary

Welcome and Opening Remarks

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

Pain affects patients across a broad range of diseases and injuries. The NIH Pain Consortium promotes collaboration across 25 NIH Institutes and Centers with programs that address pain, with the goal of advancing pain research and developing better treatments. Opioids, the most common and effective category of pain medications, carry serious risks of addiction, abuse, and death from overdose. Opioid overdose deaths have risen steadily during the past 20 years, despite attempts to intervene by changing opioid prescription practices.

Opioid treatment of pain uses neural mechanisms that overlap with reward circuitry, which creates the danger of misuse and addiction. Over-prescription of opioids has led to their misuse by some patients. In certain cases, patients seek illicit drugs such as heroin as an alternative to prescription opioids. The illegal trade of fentanyl, a compound more potent than heroin, has increased the overdose danger. Some patients who suffer from pain and are deprived of prescription opioids may seek relief through the black market.

The NIH HEAL Initiative was launched in 2018 to pursue three main goals:

- Develop safer and more effective interventions to improve pain management
- Create new medications and technologies to improve opioid addiction treatment
- Reduce the rate of overdose mortality by improving overdose reversal methods

The NIH HEAL Initiative aims to create new knowledge to meet these goals and to develop a strategy to implement new discoveries in practice. Priorities include discovering biomarkers that can be used to identify specific pain syndromes and creating a pain-based clinical trial network to accelerate the application of this knowledge in everyday pain treatment. Two fundamental questions are (1) What characterizes the transition from acute to chronic pain? and (2) Why do exogenous opioids cause tolerance while endogenous opioids do not? Finding ways to predict chronic pain development and to create opioids without tolerance effects would help to reverse the crisis by improving pain management and reducing overdose deaths.

Keynote Address: Unintended Consequences—Ensuring Access to Pain Control During an Opioid Epidemic

Judith Paice, RN, PhD, Northwestern University

The United States is experiencing a double crisis: unrelieved pain and opioid addiction. Because these crises overlap, overly simple attempts to solve one or both have created unintended consequences. Limits on opioid prescriptions have caused suffering patients to under medicate, thinking they will be denied a refill. Prescription authorizations are denied out of fear that health care providers will be held responsible for increasing opioid abuse. General restrictions on opioid access can limit the freedom of physicians to develop patient-specific treatment plans and can adversely affect patients who genuinely need relief. Conversely, some of the most effective treatments for conditions such as cancer cause pain syndromes, which are often best treated with opioids. The danger of developing an addiction can diminish the ultimate value of otherwise effective treatments.

Drug overdoses now cause more deaths in the United States than vehicle accidents and gun deaths. The rise in black market access to opioids means that limiting prescriptions will not eliminate the risk of overdose deaths and will cause suffering in many patients who experience pain. Overdose deaths began to rise in 1999 and were mainly associated with prescription opioids such as oxycodone. They rose again in 2010 with the increased prevalence of heroin abuse, and most recently again in 2013 with the spike in access to highly potent synthetic opioids such as fentanyl. The Centers for Disease Control and Prevention prescription guidelines

have curtailed opioid access and therefore have caused avoidable patient suffering, without addressing the dangers of black market synthetics. Participation in the black market of both patients desperate for pain relief and general drug users has caused confusion over who are truly the victims of the spike in opioid addiction and overdose.

Any effective solution must involve several key stakeholders, such as patients, health care providers, payers, industry, and government. Meaningful proposals must balance the subtleties of the tension between pain and addiction with the priorities of all these stakeholders. Clinicians, who are often not formally trained to treat addiction, must seek help from addiction experts. The tendency to interpret addiction as a moral failure must be overcome, just as the stigma around cancer was lifted during the 20th century. In addition, health care providers must learn to manage patient expectations. Patients should understand that a zero-pain state is often unrealistic and that healthy functioning is a more practicable goal. They should be cautioned not to use opioids as sleep aids or mood enhancers. The value of sobriety for those patients with substance use disorders approaching death should also be recognized and not diminished.

Health care providers also must learn to ask patients difficult questions to assess their risk of developing addiction. These questions might address recreational drug use, past experiences of abuse or trauma, and family history of substance misuse or abuse. If a patient's history and circumstances are evaluated through an in-depth risk assessment, treatment plans can then be tailored to their degree of risk to reduce misuse, opioid addiction and overdose. Nonpharmacological therapies and integrative treatment approaches can improve pain control, reduce patient reliance on opioids and mitigate the risk of abuse. Therefore, one important need is to expand health care system coverage and reimbursement of these alternative treatments.

Finally, reasonable solutions must account for the role played by economic despair, mental illness, and social isolation in the spread of the opioid epidemic. They must also integrate evidence-based guidelines to inform treatment plans for dealing with both chronic pain and substance abuse disorder.

Panel Session: At the Intersection of Pain, Reward and Opioids

Moderator: Rita Valentino, PhD, National Institute on Drug Abuse

Overview: Periaqueductal Gray Glia and Morphine Tolerance

Anne Z. Murphy, PhD, Georgia State University

Greater than 90 percent of chronic pain sufferers are treated with opioids. Endogenous opioid circuits, which are the target of exogenous opioids, are centered in the periaqueductal gray (PAG), a region densely concentrated with mu opioid receptors. The PAG is a critical site for opioid action in the nervous system, and its projections to the brainstem and spinal cord form the endogenous descending analgesia neurocircuit. The action of exogenous opioids, including

the development of tolerance, depends on activity occurring in the PAG and downstream along its extended circuits.

The development of opioid tolerance is significantly attenuated in chronic pain sufferers compared to persons who are not experiencing pain (i.e. recreational users). A proposed explanation is that longer-term dosing of opioids in chronic pain patients dampens debilitating pain sensations to restore homeostasis. In contrast, consumption of opioids in people not experiencing chronic pain interferes with homeostasis, and therefore the opioids are interpreted by the body as pathogens, causing an immune response. If this explanation is correct, then administration of opioids in the presence of chronic pain should not elicit an immune response, whereas blocking the immune response in non-pain conditions should attenuate tolerance. This two-part hypothesis was tested using rat models.

The first set of experiments showed that normal control rats developed opioid tolerance more readily than rats experiencing chronic pain. Control rats also showed significantly higher levels of microglia activation in the PAG, which is regarded as a physiological marker of neuroinflammation. The second set of experiments showed that activation of toll-like receptor 4 (TLR4), a pathogen detector that initiates a neuroinflammatory signaling cascade and is present in the PAG primarily on microglia, is necessary for the development of opioid tolerance. These results are consistent with the two-part hypothesis.

The action of the PAG descending analgesia neurocircuit is modulated by the inhibitory effects of GABAergic neurons in the vicinity. Acute morphine dosing hyperpolarizes these GABAergic neurons, dampening their inhibitory effects and allowing the analgesic circuitry to fire at a high rate, resulting in pain inhibition. In contrast, in the absence of pain, morphine causes more complex downstream effects, involving activation of microglia and the release of proinflammatory cytokines that lead to a significant increase in neuroexcitability. The result is a much weaker hyperpolarization of GABAergic neurons in the PAG, and a significantly reduced effect of morphine (i.e. tolerance). The attenuation in morphine's effect typically results in dose escalation, increasing the risk of overdose. Preclinical studies in rodents experiencing chronic pain have shown that co-administering morphine and a TNF biologic to block the neuroinflammation reduces morphine dosing requirements and decreases the risk of tolerance development.

Opioid-induced Plasticity and the Intersection with Pain

Jose Moron-Concepcion, PhD, Washington University

Researchers have used animal models to study the mechanisms underlying opioid-induced hyperalgesia, decreased motivation, and relapse behavior. Operant behavioral experiments that trained rats on a fixed-ratio schedule of heroin self-administration found that, after inducing paw inflammation, rats trained on relatively low doses of heroin showed decreased levels of self-dosing. However, rats trained on higher doses showed double the rate of self-administration as control rats (i.e., rats with no induced inflammation). This suggests that high doses of opioids can induce hyperalgesia and lead to overdosing in response to pain stimuli.

Researchers suspected that the relationship between pain and motivation might also play a role in governing opioid self-administration. Further experiments used self-dosing of heroin on a progressive-ratio schedule to test how far rats would go, under varying pain conditions, to obtain their opioids. Like the first experiments, rats trained on relatively low heroin doses showed decreased motivation to obtain the drug compared to controls, while rats trained on significantly higher doses displayed heightened motivation, continuing to push a lever until they received a dose. To determine whether loss of motivation to seek reward is a general effect of pain, inflamed rats and control rats were tested for motivation to receive doses of sucrose rather than heroin. The inflamed rats showed decreased motivation, suggesting a general relationship between pain and anhedonia.

Researchers hypothesized that the connection between pain and decreased motivation to seek reward involved activation of kappa-opioid receptors (KORs), which is triggered by endogenous dynorphins in the nucleus accumbens. Activation of these receptors can lead to dysphoria and anhedonia. The working hypothesis was that inducing pain increases dynorphin release, causing anhedonia and loss of motivation. Positron emission testing (PET) scans, performed on rats before and after paw inflammation, used ligands as radiotracers to visualize how readily they could bind to KORs. In inflamed rats, the ligands were largely unable to bind, indicating that KORs were already activated by endogenous dynorphins. Next, KORs were blocked with designer receptor exclusively activated by designer drugs (DREADDs), which reinstated normal motivation behavior in the rats, corroborating the hypothesis of a causal chain: pain causes dynorphin release, which activates KORs, causing anhedonia and loss of motivation. However, for rats conditioned with significantly higher doses of opioid (having thus developed hyperalgesia), the effects were different: conditioning with high doses of opioid caused increased motivation to seek the drug, which could help explain relapse behavior.

In an attempt to interrupt the relapse cycle, some researchers are using a conditioned place preference paradigm to determine how environmental cues might modulate motivation for drug-seeking in conditioned rats. Current studies use virtual reality (VR) simulations of an environment that links cues (e.g., different stripe patterns on the walls of different “chambers”) with the presence or absence of morphine. For example, in one study, rats navigate a VR environment that is projected on a screen by running on a suspended, free-floating ball while their heads are locked in place. Using a two-photon microscope, researchers can monitor their neural activity in real time and at the single-cell level. Initial results show increased firing in hippocampal region CA1 when rats enter an environment with stripe patterns previously associated with the drug, suggesting that these circuits might play a role in the creation of cues that trigger drug-seeking and relapse.

Role of Epigenetic Silencing of *OPRM1* in Opioid Tolerance in Cancer Patient Populations

Brian L. Schmidt, DDS, MD, PhD, New York University

Painful cancers such as oral squamous cell carcinoma (SCC) can be managed with exogenous opioids. But this treatment method can lead to opioid tolerance and a variety of off-target

effects such as chronic constipation. The discovery that oral cancer pain is generated peripherally in the cancer microenvironment (rather than in the central nervous system [CNS]) has spurred efforts to develop an alternative pain treatment method that avoids exogenous opioids. If endogenous opioids can be secreted by cancer cells, they could provide local analgesic effects that would avoid tolerance and other off-target effects of exogenous opioid treatment.

Because they are easily accessible, oral cancers provide a useful test case. Carcinomas such as SCC are derived from epidermal cells called keratinocytes, which contain an endogenous analgesic mechanism that is opioid based. If this analgesic system were activated, it could provide local pain relief without the use of exogenous opioids. Study of the opioid and opioid receptor expression in oral cancer cells revealed that the gene for the mu-opioid receptor, *OPRM1*, is strongly downregulated by a gene-regulatory process called promoter methylation. Methyl groups bind to CpG sites along the *OPRM1* gene within the SCC cells, leading to hypermethylation. This then suppresses the transcription of *OPRM1*, thereby canceling the production of mu-opioid receptors in cancer cells, along with their analgesic effects. The endothelin B receptor is also heavily methylated in SCC tissue, blocking the secretion of endogenous opioids.

To reverse the inhibiting effects of hypermethylation of *OPRM1*, early animal models attempted to deliver the *OPRM1* gene into cancer tissue in an immunocompromised mouse using an adenoviral vector. The transduction of *OPRM1* resulted in highly concentrated secretions of beta endorphin and significant reductions in withdrawal responses from mechanical and thermal pain stimuli. Further research applying this paradigm directly to head and neck SCCs confirmed that the antinociceptive mechanism was opioid based, which was again corroborated by the observation that naloxone effectively reversed the antinociception. The adenoviral vector was also replaced with a non-viral gene delivery method that is safer, is more selective in its action on cancer cells, and has higher transfection efficiency.

Research conducted on patients with more common cancers such as breast, colon, or prostate cancers, melanoma, or non-Hodgkin's lymphoma, separated patients into low-, medium-, and high-opioid dose groups and used a control group of patients who were prescribed but did not use opioids. Using circulating peripheral leukocytes as proxies for measurement, the researchers found that 19 of the 20 CpG sites on *OPRM1* were hypermethylated in the high-dose group.

Exposure to exogenous opioids also downregulates *OPRM1* expression in noncancer cells. Researchers have found that *OPRM1* promoters are hypermethylated—and thus downregulated—in the circulating peripheral leukocytes of males who are regularly dosed with opioids (such as those addicted to heroin). These findings suggest further reason to prefer the use of endogenous opioid systems to attenuate cancer pain. Delivering *OPRM1* directly to cancer tissue to spur the expression of mu-opioid receptors is an alternative pain management method that avoids opioid tolerance and other off-target effects of exogenous opioid therapy.

Panel Session Q&A

Participants: Anne Z. Murphy, PhD, Georgia State University; Jose Moron-Concepcion, PhD, Washington University; Brian L. Schmidt, DDS, MD, PhD, New York University

Dr. Moron-Concepcion agreed with a participant's comment that approaches to pain treatment must account for the different receptor pharmacology of different opioids. Dr. Murphy added that approaches must also consider the fact that activation patterns of different opioid receptors are very sex-dependent.

Stating that stress and pain converge on common circuits, one participant asked whether any of the investigators had replaced their experimental pain manipulations with stress to compare effects. Dr. Murphy replied that one of her early life pain studies showed that stress causes endogenous opioid release, which decreases the efficacy of exogenous opioids in the presence of pain and might be explained by an interference of receptor binding. Dr. Moron-Concepcion added that his lab is conducting experiments to better understand the relationship between stress and hyperalgesia.

Dr. Moron-Concepcion was asked whether endoscopes might create a more realistic condition for his VR experiments with rats than the fixed-head setup using two-photon microscopes. He replied that the two-photon microscope allows for monitoring of spine density levels, which makes it a superior option because spinal activity is a relevant indicator.

Dr. Schmidt was asked whether cancer's downregulation of mu-opioid receptor may have implications for cancer metastasis. He noted that cancer cells are very mobile and spread to and invade tissue. Cancer cell mobility is inhibited by the mu-opioid receptor. Thus, the downregulation of these receptors may help cancer to spread more effectively.

In reply to a question about how to choose an analgesic for orofacial pain, Dr. Schmidt highlighted the value of using local anesthetics for diagnostic purposes, because they help to locate the pain source. In cases that appear to involve the CNS and may require opioid treatment, trial and error may be necessary to identify the correct treatment and mitigate side effects for the patient.

Mitchell Max Junior Investigator Presentations

Introduction of Junior Investigator Presentations

Patricia A. Grady, PhD, RN, FAAN, Director, National Institute of Nursing Research

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.

A Mouse Pain Scale: Assessment of Pain Sensation in Mice Using Sub-Second Behavioral Mapping and Statistical Modeling

Ishmail Abdus-Saboor, PhD, University of Pennsylvania

Laboratory studies often rely on subjective methods such as pain scale questionnaires to assess pain states in experimental subjects. These methods have some inherent drawbacks: they are difficult to interpret and compare objectively; they cannot be used for some people, including young children and people in altered states; and they are impossible to use with animal subjects. Animal researchers use a variety of pain assessment assays that measure behavior as a proxy to circumvent these limitations. The most common assay in mouse research measures the paw withdrawal reflex to infer pain states. However, because this method typically provides researchers with an overly simplified binary distinction between present or absent paw withdrawal, researchers have developed a new method to enrich data from paw withdrawal assays.

The main innovation is to use high-speed videography (1,000 frames/sec) to capture fine details in the physiological responses of mice to different mechanical stimuli. Instead of a binary distinction between "withdrawal" and "no withdrawal," more information is collected through capture of a wider range of features. Jumping, paw guarding, orbital tightening, paw shaking, the temporal sequence of head movements and paw movements, and other behaviors are analyzed in combination to develop a detailed data set. These data are correlated alongside neural calcium activation patterns to confirm that touch neurons and nociceptors are being selectively activated by different stimuli. With biostatistics, the data for behavioral reactions to these stimuli are then run through a principal component analysis that weights the various movement parameters to form a continuous scale.

Each instance of mechanical stimulation is located somewhere on the continuum using a principal component score. The means of principal component scores across experimental and control conditions fall either above zero (pain response) or below zero (non-pain response), with distance from the zero-point indicating the magnitude in either direction.

Researchers conducted two experiments to test the usefulness of the principal component score. They designed a learning platform to predict which stimuli should, on average, result in a positive versus a negative principal component score. The first experiment used three common Von Frey Hair fibers to test the probabilistic predictions of the machine learning platform. The second experiment used optogenetic techniques to selectively activate nociceptors under various conditions and to compare results to the machine learning predictions. In both experiments, the means of the actual principal component scores were sufficiently similar to the machine learning predictions to indicate the reliability of the principal component score as an objective pain scale in rodent pain behavior assays.

Cdk5 Inhibitory Peptide TFP5 Attenuates Acute Orofacial Inflammation and Reduces the Severity of Mechanical Allodynia

Michaela Prochazkova, PhD, National Institute of Dental and Craniofacial Research

Cyclin-dependent kinase 5 (Cdk5) is an enzyme that is expressed throughout the body but is not active in its monomer form. It acquires binding potential when it is activated by one of two proteins, p35 or p39. Cdk5 plays a role in many physiological processes, including pain signaling. Research has demonstrated that mice that specifically lack p35 (but not p39) show significantly lower sensitivity to nociceptive orofacial mechanosensation and chemosensation, implying that p35-activated Cdk5 is associated with orofacial pain signaling. Lack of p35 thus inhibits Cdk5 activation, causing analgesia.

These results suggest that Cdk5 inhibitors may produce analgesic effects in patients with orofacial inflammation, but commercially available Cdk5 inhibitors lack specificity and cause unwanted side effects. However, a Cdk5 inhibitory peptide called TFP5, discovered in another lab, inhibits abnormal hyperactivity of Cdk5—a cause of mechanical allodynia, which is an abnormal sensitization of nociceptors following mechanical stimulation—without affecting other Cdks. Further experiments demonstrated that TFP5 reduced Cdk5 hyperactivity in vitro and in the trigeminal ganglia after the induction of orofacial inflammation during animal trials.

Researchers then designed a model in which mice gnawed through two dowels (first soft, then hard) to escape their cages. The time required to gnaw through hard dowel was measured as a proxy for orofacial sensitivity to mechanical stimulation, and thus of orofacial pain experience. Mice treated with the TFP5 inhibitory peptide spent significantly less time gnawing through the dowels, suggesting that the downregulation of Cdk5 by TFP5 had a strong analgesic effect on orofacial inflammation and mechanical allodynia.

Neural Dopamine: Unraveling the Mechanisms of Stimulant-Induced Analgesia and Arousal

Norman Taylor, MD, Massachusetts General Hospital

Dopaminergic circuits are known to affect locomotion, reward, and cognition. More recently, dopamine systems have also been linked to analgesia and arousal. Research conducted on orthopedic and general surgery patients revealed that dextroamphetamine (D-amphetamine, a CNS stimulant) led to heightened post-operative alertness and pain relief when administered with opioids. However, the underlying mechanism was not well understood.

The knowledge that D-amphetamine is a dopamine receptor agonist led researchers to question whether dopamine agonists alone could induce analgesic effects without accompanying opioids. Mouse models showed that analgesia induced with only D-amphetamine was as effective as morphine; but the specific mechanism remained unknown. Further research revealed that c-FOS expression is elevated (indicating heightened neural firing) and colocalized with dopamine neurons in the PAG . These neurons extend to the ventral tegmental area (VTA), the amygdala, and the nucleus accumbens, which could help to explain

the mechanism underlying the analgesic effects of D-amphetamine. Next, researchers used designer receptors exclusively activated by designer drugs (DREADDs) to precision-target dopamine neurons in the PAG, causing them to produce receptors that were then activated by specific ligands. This method produced analgesic effects that mirrored those of opioids.

Aside from analgesia, the neural mechanism underlying heightened post-operative alertness in surgery patients who received D-amphetamine was also poorly understood. To investigate, researchers placed mice under a constant dose of general anesthesia on their backs. When D-amphetamine, methylphenidate, or a specific D1 receptor agonist was administered, mice flipped onto their feet, recovered normal motor function, and showed elevated respiration rates even as anesthesia dosing remained constant. Subsequent trials using only electrical stimulation of the VTA achieved the same effect.

However, electrical stimulation does not target specific neuron types. Therefore, researchers repeated trials using optogenetics to selectively target dopamine neurons, which produced the same effect. The sedating effect of constant dosing with general analgesia was overcome by activating dopamine neurons in the VTA. Because this effect might have been due to the activation of locomotive neurons, rather than an arousal response, further trials incorporated learning assessments to distinguish locomotion from an arousal response. The mice retained learning they developed during earlier trials, even in the presence of continued administration of general anesthesia. These results show that the effect is explained by arousal, but not by simple locomotion.

In summary, in addition to the three functions usually associated with dopamine (locomotion, reward, and cognitive function), analgesia and arousal are also modulated by dopaminergic systems. This knowledge could inform development of new methods to modulate pain.

Featured Presentation

Walter Koroshetz, MD, Director, National Institute of Neurological Disorders and Stroke, introduced Francis Collins, MD, NIH Director. Almost 1 year ago, Dr. Collins picked up the gauntlet to place NIH at the forefront of the fight against the dual crises of chronic pain and opioid addiction.

Dr. Collins described the NIH HEAL Initiative, which was launched in April 2018 to speed scientific solutions to stem the national opioid public health crisis. Congress has appropriated an additional $500 million per year in the FY18 Omnibus legislation to enable NIH to expand its efforts to address this emergency. Before HEAL was launched, NIH already supported efforts to pursue research in pain management, overdose reversal, and opioid addiction treatment.

Six research priorities have been selected for HEAL in 2018, three of which are specifically focused on pain research: (1) understand the neurobiology of chronic pain, (2) develop new non-addictive treatments for pain, and (3) build a Clinical Trials Network for chronic pain.

Past research supported by NIH has led to several contributions. These include Food and Drug Administration–approved drugs such as Narcan and Vivitrol, a buprenorphine arm implant

known as Probuphine, and new strategies to activate mu-opioid receptors that do not cause tolerance or addiction. Basic research findings, such as the critical role of the SCN9A channel in pain sensation coming out of genetic studies, may lead to entirely novel targets for non-addictive pain medications. With the launch of HEAL, the scope of these activities will expand significantly to range from basic research to clinical trials. In addition, studies will be conducted across agencies, sectors, organizations, and industry in large-scale partnerships to foster rapid progress.

Dr. Collins highlighted the important roles of academia in early target discovery and of academia-industry partnerships in the translational process, as well as the opportunity to work with industry to move compounds into real-world use that have shown to be safe and effective but have been abandoned for commercial reasons.

Achieving the translational goals of HEAL will allow physicians to target chronic pain with non-addictive drugs and other, integrative therapies. The faster completion of clinical trials testing of these drugs and therapies is a high priority.

Fireside Chat: Pain and Public Perceptions

Vice Admiral Jerome Adams, MD, MPH, U.S. Surgeon General; Francis Collins, MD, PhD, Director, National Institutes of Health

The U.S. Surgeon General is responsible for disseminating key medical knowledge and for helping to implement policies that improve health outcomes for Americans. Five themes emerged from the Fireside Chat that highlight the intersection of these responsibilities with the Symposium's agenda.

Translate research into health

Sufferers of pain and addiction rely on continuous research to develop new drugs and non-pharmacological therapies. However, much of the knowledge gained about how best to fight pain and the opioid crises is not applied in practice quickly enough. Researchers could drive "implementation science" to accelerate the practical application of benefits from new scientific discoveries.

Make Naloxone as commonly available as cardiopulmonary resuscitation

Offering an example of an action that anyone can take to counteract the opioid crisis, the Surgeon General urged Symposium participants to always carry naloxone, an opioid antidote that can save lives in cases of acute overdosing. He hopes that this life-saving intervention will help most of today's victims, who overdose outside of a medical facility, and will become as commonly known as CPR.

Recognize that stigma contributes to patient deaths

Across the United States, especially in rural areas, stigma causes unnecessary deaths. The belief that pain is "just something you have to deal with," or that addiction is a moral failure, discourages people from seeking treatment. Stigma also creates taboos around some forms of therapy or relief (e.g., methods for training resilience or practicing mindfulness) that could

decrease pain patients' reliance on opioids. If stigma persists, then unnecessary suffering and addiction, pain, and even death will also persist. Conversely, exaggerated fears of addiction can lead to restricted access to opioids for patients who genuinely need relief from intense chronic pain.

Acknowledge and explore the link between pain, addiction, and mental health
Untreated mental health issues can lead to addictive and criminal behavior. A substantial portion (30 percent) of chronic pain patients have a history of posttraumatic stress disorder (PTSD), and a history of childhood trauma can lead to addiction. While we cannot eliminate all trauma, we can improve our understanding of resilience and support systems to build emotional and spiritual resilience. Pilot studies should explore how mental, emotional, and spiritual components can be integrated to fight against chronic pain and addiction.

Achieve better health through better institutional partnerships
Better institutional partnerships can create new incentives to push action toward achieving desired outcomes. Collaboration between government entities, private partners, faith communities, and other research and policy bodies can advance new efforts in pain and addiction research, including implementation science and overcoming of stigmas and taboos. New incentives can shift the paradigm from paying for medications and procedures to paying for desirable health outcomes.

The Surgeon General encouraged the audience to seize the opportunities that the current media attention to the opioid crisis brings to the field of pain research. He warned against an overly mechanistic view of pain with a too narrow focus on new drug treatments and encouraged development of a view that accounts for the biological, emotional, and spiritual components of pain and offers a broad range of interventions. To ensure that these interventions become widely available, value-based payment models are needed.

Panel Session: The BRAIN Initiative: Harnessing Technology for Pain Research

Moderator: Khara Ramos, PhD, National Institute of Neurological Disorders and Stroke

Overview: The BRAIN Initiative and Pain

Walter Koroshetz, MD, Director, National Institute of Neurological Disorders and Stroke

The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is a major collaboration aimed at increasing knowledge about the brain by pursuing the development of new technologies that advance brain science. Projects funded by the BRAIN Initiative began in 2014 and have generated more than 330 publications to date. The underlying motive of the initiative is to improve the ability to monitor and modulate neural circuit activity, which has clear applications for pain research, diagnosis, management, and alleviation.

The BRAIN Initiative pursues several research avenues, including neural recording and modulation, human imaging, and detailed circuit mapping. It seeks to characterize every cell

type in the brain and to develop tools that will enable monitoring, diagnosis, and intervention at changing levels of precision, from the firing of individual neurons and whole populations of cell types, to their integrated firings across whole brains. For example, genetic tools are now available that cause specific cell types to light up while active, which allows for detailed monitoring of neural activity and new ways to detect malfunction. Such tools could lead researchers to design medicines to act on specific cell types.

The proliferation of cell-based tools for brain monitoring and modulation holds promise for pain research. A detailed mechanistic understanding of pain circuit activity in the brain and spinal cord can be integrated with patient reports to achieve a more comprehensive understanding of the pain experience and can enable precise intervention methods that provide more effective and targeted relief. As the BRAIN Initiative proceeds, a major task will be to develop tools to help analyze and interpret the large stores of data that these advanced tools generate.

Radiomagnetogenetics

Sarah Stanley, MBBCh, PhD, Icahn School of Medicine at Mount Sinai

Pain sensations are caused by energetic firing of pain neurons. Dampening the activity of pain neurons, or activating neurons that inhibit them, can attenuate their effect and relieve pain. Researchers have developed a new genetics-based method to remotely control neural firing in pain circuits. Radiomagnetogenetics was created as an alternative to optogenetics and chemogenetics and combines the advantages of both. It is cell-specific, has a rapid onset, can be used to activate or silence local or widespread cell populations, and does not require a permanent implant.

Radiomagnetogenetics works by controlling the opening and closing of the TRPV1 ion channel in the membrane of target neurons. The system has three components, the first of which are radio waves, which act as the remote signal. The second component is a genetically modified ferritin protein within each target cell. Ferritin consists of iron oxide nanoparticles that can be modified to include a green fluorescent protein (GFP) tag that can absorb the energy from incoming radio waves. The third component is the TRPV1 channel itself, which is modified to include an anti-GFP nanobody on its end terminal. This nanobody tethers the channel to the GFP-tagged ferritin.

When the radio signal is turned on, the GFP-tagged ferritin absorbs the radio wave energy. That energy is then transferred by the anti-GFP nanobody to the TRPV1 channel, which opens. This in turn lets sodium and calcium into the cell, causing depolarization. Further studies showed that TRPV1 can be made selectively permeable to calcium and that the resulting depolarization can become strong enough to activate nerves. Using this method in mice to stimulate glucose-sensing neurons in the ventromedial hypothalamus led to upregulation of blood glucose, with increasing field strength causing increasingly high glucose levels. These findings show that radiomagnetogenetics can be used to remotely activate specific neural populations with a titratable effect. The same mechanism can be used to silence neurons. To achieve silence, an

induced mutation modifies the TRPV1 channel to become selectively permeable to chloride (instead of sodium and potassium), which causes cell hyperpolarization and silencing.

The prevailing explanation of how this mechanism works centers on the ferritin protein. It is believed that the iron oxide subunits, which fit together to form ferritin, are normally in a state of magnetic entropy—that is, the magnetic fields of the subunits are disorganized. When radio waves strike the ferritin, the disorganized fields align, which releases heat energy. This expelled heat energy is transferred by the anti-GFP nanobody to the TRPV1 channel, which then opens.

It remains unknown whether use of this mechanism can lead to tolerance. Although delivering the neuromodulatory construct is invasive, the remote signal is not. Further research is needed to determine the technique's clinical potential. Using this method to either silence nociceptors or raise their activation thresholds may, one day, become an effective therapy for pain patients.

Spinal Cord Stimulation to Restore Sensation and Reduce Phantom Limb Pain After Limb Amputation

Lee Fisher, PhD, University of Pittsburgh

Of the 1.5 million Americans who have suffered limb amputations, 85 percent of them experience phantom limb pain. This condition, which causes amputees to experience pain emanating from the absent limb, is believed to result, in part, from sensorimotor incongruence. Cortical plasticity causes modification of the somatosensory brain regions responsible for receiving information from the missing limb. Signals between sensory and motor systems in the patient's cortical map then become mismatched, leading to painful sensations. Phantom limb patients, who often describe sensations of burning, cramping, throbbing, piercing, and tingling, can suffer significant dysfunction due to debilitating pain.

Phantom limb pain is usually difficult to treat, with techniques like electrical spinal cord stimulation, providing relief in some patients, but typically only for a few years. Recent work seeks to alleviate long-term phantom limb pain by delivering sensory input that is localized to specific regions of the phantom limb to reestablish sensorimotor congruence and improve patient functioning. Experiments conducted with patients with arm amputations above the elbow have shown that sensations can be induced that register at the level of individual fingers. When subjects are asked to describe these sensations, the most common tags are electrical, vibration, and pressure. By varying the pattern of stimulation, researchers can induce more natural sensations. In addition, advanced prosthetics can convey information to the brain about what the prosthetic limb is doing. This information can be fed back into neural motor commands, helping to reestablish normal sensorimotor congruence.

The key question for pain researchers is how these interventions can affect phantom limb pain. In one study, every time patients received electrical stimulation, they were asked about the intensity of the stimulation and of their phantom pain. Initial findings indicate that patients experienced heightened phantom pain in response to electrical stimulation. However, when collected over 1 month, McGill Pain Questionnaire results indicate that the initial experience of heightened phantom pain dissipates and eventually the pain becomes lower than initial levels.

The prevailing explanation for this delayed effect is that people with amputations typically try to ignore their phantom pain, but in these experimental settings they are asked to attend to it. If this is the case, then patients' immediate experience of phantom pain would intensify, but then dissipate over time.

Efforts to further improve sensorimotor congruence and thus alleviate phantom pain have used VR technology to provide phantom limb patients with realistic visual sensations of the missing limb. This information can then be integrated with sensations from the phantom limb caused by lateral spinal cord stimulation and with haptic sensations from advanced prosthetics. This threefold combination of sensorimotor information creates mutual sensory feedback that improves signal integration and relieves pain. The next step in this research will seek to extend these results with upper limb amputation patients to lower limb amputation patients.

Panel Session Q&A

Participants: Walter Koroshetz, MD, Director, National Institute of Neurological Disorders and Stroke; Sarah Stanley, MBBCh, PhD, Icahn School of Medicine at Mount Sinai; Lee Fisher, PhD, University of Pittsburgh

In response to a question about publications, Dr. Fisher noted that the upper limb amputation work should be published by the end of 2018, but the lower limb amputation work is just beginning. Dr. Stanley noted that her CNS work in radiomagnetogenetics was published in 2016, and the peripheral nervous system (PNS) work is ongoing.

Dr. Fisher responded to a question about whether different kinds of injuries or diseases that lead to amputations result in different kinds of phantom limb pain. Because the pain is largely mediated by proximal regions of the PNS, which are essentially normal even in amputees, the phenomenon of phantom limb pain is very similar across patients.

One participant asked Dr. Fisher whether his team has considered integrating psychological approaches to pain modulation into its methods. Although it has not, Dr. Fisher acknowledged that such integration might yield interesting results. For example, there may be psychological methods to help patients embody their prosthetics rather than view them as tools, which might improve sensorimotor signal integration and thus attenuate phantom pain.

Dr. Fisher was asked whether his team has conducted VR reality trials with a control condition that does not include spinal cord stimulation. He replied that the short time frame currently available for these trials (29 days) has precluded his team from doing so.

Replying to a question about whether endogenous ferritin levels are sufficient for radiomagnetogenetics to work, Dr. Stanley cited a research team at Duke University that successfully performed a technique like the one she described without artificially raising ferritin levels in target cells. Her team is exploring this concept further, because it might allow for a smaller construct.

When asked about the pain conditions she would focus on to advance understanding of how radiomagnetogenetics can work in the PNS, Dr. Stanley noted her priority of targeting peripheral conditions and improving the ability to target the vector to specific peripheral regions such as the dorsal root ganglia.

In response to the final question, Dr. Stanley stated that radiomagnetogenetics has not been tested in glial cells. However, because glial cells play a prominent role in some conditions such as metabolic disease, this approach would be worth investigating.

Mitchell Max Award Presentation

David Shurtleff, PhD, Acting Director, National Center for Complementary and Integrative Health

The 2018 Mitchell Max Award was awarded to Dr. Ishmail Abdus-Saboor for his presentation titled "A Mouse Pain Scale: Assessment of Pain Sensation in Mice Using Sub-Second Behavioral Mapping and Statistical Modeling." Dr. Abdus-Saboor earned a BS in animal behavior from North Carolina A&T University and a PhD in molecular biology from the University of Pennsylvania. He won several NIH grants as a postdoctoral fellow and will start work as an assistant professor in the Department of Biology at the University of Pennsylvania in July 2018.

Day 2 Meeting Summary

Update from the American Pain Society

William Maixner, DDS, PhD, Duke University, President, American Pain Society, Co-director, Duke Center for Translational Pain Medicine

The American Pain Society (APS), founded in 1977, is a multidisciplinary community of scientists, clinicians, and other professionals that aims to increase knowledge of pain and transform public policy and clinical practice to reduce pain-related suffering. The NIH HEAL Initiative provides new opportunities for APS to partner with the U.S. Department of Health and Human Services to reverse the opioid epidemic. APS concentrates on research, education, patient management, and advocacy. Its main research goals are to:

- develop novel treatments that enhance clinically meaningful pain relief and functional improvement with acceptable adverse effects;
- expedite progress toward the prevention, diagnosis, and management of chronic pain;
- optimize the use of and access to currently available and effective treatments;
- understand the impact of health policies and systems on pain treatment; and
- improve pain management through education research.

Another priority of APS is to disseminate new knowledge generated by pain research, primarily through publishing *Journal of Pain* and by hosting the APS annual meeting. The next meeting will be held in Milwaukee, April 3-6, 2019.

A Patient's Perspective

Proper Pain Diagnoses, Treatment, Effect, Understanding, and the Opioid Guideline Backlash

George Carter, Sickle Cell Patient and Advocate

Patients with sickle cell disease and other conditions linked to chronic pain have become the unintended victims of anti-drug policies. Federal and state guidelines and limitations on opioid prescriptions have created a climate of fear in which physicians are reluctant and sometimes refuse to treat severe pain with opioids, which are often the only available and effective option for relief.

Chronic and extreme pain can interfere with normal functioning and can exercise control over many facets of a patient's life. Doctors should aim to thoroughly diagnose pain by differentiating its causes and symptoms and by assessing its severity objectively, because patients who have lived with pain for a long time may inadvertently conceal the magnitude of their suffering.

Most overdose deaths occur with illegal opioids. Aiming to reverse the addiction crisis by restricting opioid access to patients with chronic and extreme pain misses the target and has serious negative consequences for those who urgently need relief.

"We who suffer in pain are the casualties or unintended victims of the War on Drugs. The opioid crisis is already creating a pain management crisis. Where do we go from here?"

Panel Session: Disparities in Clinical Pain Management

Moderator: Eliseo Peréz-Stable, MD, Director, National Institute on Minority Health and Health Disparities

From 2000 to 2015, drug overdose deaths increased for blacks, Latinos, whites, Native Americans, and Alaskan Natives, with the latter two groups shouldering a disproportionate burden. Among black Americans, cocaine causes more deaths than any other drug. The opioid epidemic appears to be a part of a larger addiction epidemic.

Limited data from emergency departments has shown that minorities are prescribed opioids at lower rates than whites and have less access to opioids for pain relief. Although the data from primary care settings are too limited to warrant any conclusion, the prevailing explanation for these trends has been that bias causes doctors to more readily assume that minority patients are drug-seekers. The panelists described efforts to explain disparities in pain management.

Overview: Differences in Opioid Prescribing by Specialty and Demographics

Asheley Cockrell Skinner, PhD, Duke University

Research has revealed demographic differences in opioid prescription rates. Most studies to date have considered who the patients are and where they are treated, in terms of geography

and care setting. Women tend to receive more opioids than men, and the young tend to receive more than the old. However, most research has focused on racial disparities, particularly between white and black patients.

For example, in emergency pain treatment, white patients are more likely to receive opioids than black or Hispanic patients for undefined pain such as migraines or back pain. However, in cases of better-defined pain (e.g., long bone fractures), no disparity in opioid prescription rates has been found. White patients are also more likely to receive opioids in outpatient settings, while black patients who do receive opioids are more likely to be subjected to risk reduction strategies such as urine testing and early refill restrictions.

Behavioral explanations do not appear to account for these racial disparities because racial differences in opioid prescriptions are observed even for children with appendicitis. More likely explanations include bias, differences in availability of pharmacies and alternative treatments, and communication barriers between patients and their providers.

Limited findings on geographical disparities suggest that rural residents are more likely than urban residents to be prescribed opioids. In addition, patients living in locations with higher concentrations of pain specialists are less likely to receive high-dose or long-term opioid prescriptions. Differences in access to alternative treatments may partially explain these findings. There is significant regional variance in high-dose versus long-term prescriptions, which raises questions about which specialties are prescribing at what rates. Overall opioid prescription rates are increasing, with the highest increases in rehabilitation and pain medicine and a more modest increase in general practice. However, prescription rates are decreasing in some specialties, especially surgery, dentistry, and emergency medicine.

Understanding Adverse Selection: The Role of Mental Health in Opioid Therapy for Chronic Pain

Mark Sullivan, MD, PhD, University of Washington, Seattle

Adverse selection occurs when patients with a heightened risk of developing an opioid abuse disorder are also more likely to be exposed to that risk. Research suggests that patients with risk factors (e.g., mental health or substance abuse disorders) are more likely to be prescribed high-risk opioid regimens and to end up abusing their medication. The concept that policies regulating opioid prescription must balance pain treatment with addiction avoidance mis-frames the issue. It overlooks the interaction of mental health and opioid addiction, which is fueled by adverse selection and underlies the opioid epidemic.

One reason for the neglect of this interaction is that controlled trials of opioid therapy for chronic non-cancer pain patients has excluded subjects with mental health or substance abuse disorders. Therefore, the evidence guiding prescription practices does not account for these patient groups. Meanwhile, adverse selection occurs with a variety of mental health and substance abuse disorders. A concrete example is the self-selection for opioid therapy of chronic pain patients with depression. These patients are only slightly more likely to initiate opioid therapy, but once initiated are twice as likely to transition to long-term use. They

continue using opioids at lower pain thresholds to treat insomnia, stress, and depression itself. There is also evidence that long-term opioid therapy causes incident, recurrent, and treatment resistant depression. Opioids thus become the cause and the consequence of depression for these patients, which fuels the cycle of abuse.

Findings show consistent patterns of adverse selection when high-risk patients are placed on high-dose opioid regimens. Similar and even more pronounced patterns are evident for opioid/benzodiazepine co-prescription, especially in patients who suffer from posttraumatic stress disorder (PTSD). Because the physical survival of mammals often depends on social functioning, endogenous opioids evolved in mammals not only to modulate pain but also to modulate social stress and facilitate the formation and maintenance of social bonds. In patients with PTSD, exogenous opioids may help to reduce re-experiencing and hyperarousal but deepen numbing and avoidance, thereby prolonging PTSD and exposing patients to significant overdose risk.

Patients with PTSD who are prescribed opioids for chronic pain sometimes self-medicate for psychosocial distress, leading to an opioid abuse disorder. Therefore, attempts to restrict the use of opioids to exclusively treat chronic physical pain cannot succeed. Because the endogenous opioid system evolved to perform stress-modulating functions other than relieve physical pain, patients will tend to use opioids to treat psychological conditions. Similar effects for a variety of mental health and substance abuse disorders appear to underly the phenomenon of adverse selection in opioid prescription.

Using Interactive Virtual Humans to Improve Pain Care for Racial Minority and Low-Income Patients

Adam T. Hirsh, PhD, Indiana University – Purdue University, Indiana

Racial and ethnic disparities are well documented in pain care but remain largely unexplained. Common explanations for the disparities include patient, socio-contextual, and provider factors, but existing data are mixed and thin. Better understanding of the underlying factors is needed to design and deliver effective interventions. Researchers have begun to study how provider factors such as attitudes, beliefs, stereotypes, and biases, as well as their comfort level interacting with patients of different cultural and social groups (i.e., intergroup anxiety), may help explain these disparities. Two questions drive these studies: (1) Is intergroup anxiety affecting the way doctors treat their patients' pain? and (2) If yes, can interventions be developed to reduce intergroup anxiety?

Patients and providers often live in different neighborhoods and belong to different demographic, cultural, and community groups. Meta-analysis of more than 500 studies shows that empathy and trust between groups increase with intergroup contact, while anxiety and perception of threat decrease. These positive effects can be achieved through live and imaginal interactions, and possibly through virtual interactions.

To test a new intervention using virtual patients to facilitate intergroup contact and reduce disparities in pain treatment, a group of physicians underwent an initial bias assessment. Those

who showed signs of treatment bias were randomized to an intervention or control group. The intervention group received real-time feedback about their bias, engaged in one-on-one interactions with virtual patients, and watched VH videos to facilitate intergroup contact and perspective-taking. Both the intervention and control groups were reassessed for treatment bias one week later. Compared to the control group, physicians who underwent VH intervention had 85 percent lower odds of being biased against black patients and 73 percent lower odds of being biased against low socioeconomic status patients upon reassessment.

In addition to reducing physician intergroup anxiety and enhancing perspective-taking, pain treatment disparities might be alleviated by helping patients to more effectively engage in shared decision making (SDM) with their providers. SDM requires that patients clarify their values regarding their own health and functioning, understand the pros and cons of different treatment options, and effectively communicate with their providers. A new intervention called *Goal Elicitation, Treatment Prioritization, and Electronically-Practiced Discussion (GET PrEPD)* is being developed to help minority patients clarify their values, determine their treatment preferences, and improve their communication skills by having them interact with VH providers. The objective is to encourage understanding and collaboration between minority patients and their providers by helping patients to form and effectively communicate their own health goals and treatment preferences.

Insights into Ethnic Differences in Pain from Experimental Studies

Claudia Campbell, PhD, Johns Hopkins University

Researchers have observed differences in pain experience across ethnicities in clinical settings. However, several clinical variables contribute to the challenge of determining the mechanisms for group differences. Quantitative and experimental pain testing aims to understand these differences through controlled studies that attempt to avoid confounding clinical variables. The findings may help to identify mechanisms for group differences, patients at risk of developing chronic pain, and to determine which analgesic interventions will be most effective for specific patients or patient groups.

Overall, past experiments indicate that minority groups (blacks are the most commonly tested) tend to have lower pain thresholds than whites. These experiments largely used static measures (i.e., single points along a pain threshold continuum) that are stable but potentially overly simplistic. Dynamic measures that assess multiple data points (e.g., changes in pain experience over repeated stimuli) are becoming more common. One dynamic measure is Conditioned Pain Modulation (CPM), where one pain sensation becomes attenuated when another is introduced. The effect is at least partly physiological and involves endogenous opioids. Researchers have found that participants with low CPM, which implies poor endogenous opioid tone, are significantly more likely to develop chronic pain a full year after surgery.

To improve the ability to compare pain symptoms and vulnerabilities across ethnic groups, researchers have developed a method called nociceptive profiling. This method combines results of laboratory pain measures, including CPM data, to distinguish participants with pro-

and anti-nociceptive profiles. These categories are thought to reflect a distinction of CNS sensitization to pain activation.

Heightened CNS sensitization is associated with many pain conditions (e.g., fibromyalgia, migraine, sickle cell disease). The study of ethnic differences in pro- versus anti-nociceptive profiles is in the very early stages. To date, results indicate noticeable differences between non-Hispanic black and non-Hispanic white participants, with blacks showing an overall pro-nociceptive profile and whites showing an overall anti-nociceptive profile. Researchers intend to expand efforts to discover whether ethnic differences in nociceptive profiles and CNS sensitization can predict a patient's chances of developing chronic pain, and whether personalized interventions that use medications and modifiable risk factors (e.g., sleep, mood, exercise) can increase endogenous opioid tone, forestall pain, and achieve relief.

Panel Session Q&A

Participants: Asheley Cockrell Skinner, PhD, Duke University; Mark Sullivan, MD, PhD, University of Washington, Seattle; Adam T. Hirsh, PhD, Indiana University – Purdue University, Indiana; Claudia Campbell, PhD, Johns Hopkins University

In response to a question about disparities in access to non-pharmacological treatments (e.g., physical therapy, massage, chiropractic treatment), Dr. Skinner agreed that access plays a major role in the disproportionate suffering of people in low socioeconomic status and rural areas from the drawbacks of opioid therapy.

Dr. Sullivan referred to a Princeton study showing that white people in rural areas also disproportionately suffer from "diseases of despair" that are connected to drug and alcohol abuse. These phenomena cannot be understood without separating the different variables, which is difficult to do.

When asked whether it is justified to infer a causal relationship from an association between opioid/benzodiazepine co-prescription and overdose, Dr. Sullivan acknowledged that the association does not conclusively demonstrate causation, but that a causal relationship seems to be the best explanation given the strength of the association.

A participant asked whether the categories of "addiction" and "dependence" could be misleading. Dr. Sullivan agreed that the overlap between these categories must be acknowledged and suggested that the field has not caught up with the populations who were exposed to opioids at unprecedented levels beginning in the mid-1990s.

Another participant asked Dr. Hirsh whether the demographic features of providers predict any measurable biases. Dr. Hirsh noted that a member of his research team has provided some preliminary data that suggest the non-significance of provider demographics. However, he stressed that these analyses are cursory and the data need to be reviewed more carefully.

Dr. Hirsh also responded to a question about cultural differences in pain perception. Regarding each patient as a rational agent who will experience an objective rise in nociceptive activity as a

subjective rise in pain, and who will then seek analgesia, may be a mistaken assumption that obscures cultural differences in how individuals respond to variation in pain.

Closing Remarks

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

NIH will continue to press the agenda to improve pain management, overdose reversal, and opioid addiction treatment through the NIH HEAL Initiative and will pursue Vice Admiral Adams' call to produce better medicine through better partnerships.

Dr. Somerman closed this year's Symposium by thanking all presenters, speakers, and panelists and by acknowledging Dr. Cheryse Sankar from the NIH Office of Pain Policy and Dr. Yolanda Vallejo from the National Institute of Dental and Craniofacial Research (NIDCR) for organizing the event.

Appendix 1: Agenda

May 31, 2018

8:30 AM **Welcome and Opening Remarks**
Nora Volkow, M.D., Director, National Institute on Drug Abuse

8:50 AM **Introduction of Keynote Speaker**
Ann O'Mara, Ph.D., R.N., FAAN, National Cancer Institute

Keynote Address: Unintended Consequences: Ensuring Access to Pain Control During an Opioid Epidemic
Judith Paice, R.N., Ph.D., Northwestern University

9:45 AM Poster Session and Break

10:15 AM **Panel Session: At the Intersection of Pain, Reward and Opioids**
Moderator: Rita Valentino, Ph.D., National Institute on Drug Abuse

Overview: Impact of Sex and Age on Opioid Modulation of Pain
Anne Z. Murphy , Ph.D., Georgia State University

10:45 AM **Opioid-induced Plasticity and the Intersection with Pain**
Jose Moron-Concepcion, Ph.D., Washington University

11:05 AM **Role of Epigenetic Silencing of *OPRM1* in Opioid Tolerance in Cancer Patient Populations**
Brian L. Schmidt, D.D.S., M.D., Ph.D., New York University

11:25 AM **Panel Session Q & A**

11:45 AM Poster Session and Lunch

1:00 PM **Mitchell Max Junior Investigator Presentations**
Introduction of Junior Investigator Presentations
Patricia A. Grady, Ph.D., R.N., FAAN, Director, National Institute of Nursing Research

1:10 PM **A Mouse Pain Scale: Assessment of Pain Sensation in Mice Using Sub-second Behavioral Mapping and Statistical Modeling**
Ishmail Abdus-Saboor, Ph.D., University of Pennsylvania

1:25 PM **Cdk5 Inhibitory Peptide TFP5 Attenuates Acute Orofacial Inflammation and Reduces the Severity of Mechanical Allodynia**
Michaela Prochazkova, Ph.D., National Institute of Dental and Craniofacial Research

1:40 PM **Neural Dopamine: Unraveling the Mechanisms of Stimulant-Induced Analgesia and Arousal**
Norman Taylor, M.D., Massachusetts General Hospital

1:55 PM **Introduction of Featured Presentation**
Walter Koroshetz, M.D., Director, National Institute of Neurological Disorders and Stroke

2:00 PM **The NIH HEAL Initiative**
Francis Collins, M.D. Ph.D., Director, National Institutes of Health

2:15 PM **Fireside Chat: Pain and Public Perceptions**
Vice Admiral Jerome Adams, M.D., M.P.H., U.S. Surgeon General
Francis Collins, M.D. Ph.D., Director, National Institutes of Health

2:45 PM **Q & A**

3:00 PM Poster Session and Break

3:25 PM **Panel Session: The BRAIN Initiative: Harnessing Technology for Pain Research**
Moderator: Khara Ramos, Ph.D., National Institute of Neurological Disorders and Stroke

Overview: The BRAIN Initiative and Pain
Walter Koroshetz, M.D., Director, National Institute of Neurological Disorders and Stroke

3:40 PM **Radiomagnetogenetics**
Sarah Stanley, MBBCh, Ph.D., Mount Sinai Medical Center

4:00 PM **Spinal Cord Stimulation to Restore Sensation and Reduce Phantom Limb Pain after Limb Amputation**
Lee Fisher, Ph.D., University of Pittsburgh

4:20 PM **Panel Session Q & A**

4:35 PM **Mitchell Max Award**
David Shurtleff, Ph.D., Acting Director, National Center for Complementary and Integrative Health

4:50 PM Adjourn

June 1, 2018

8:30 AM **Update from the American Pain Society**
William Maixner, D.D.S., Ph.D., Duke University

8:50 AM **A Patient's Perspective**
Proper Pain Diagnoses, Treatment, Effect, Understanding, and the Opioid Guideline Backlash
George Carter, Sickle Cell Patient and Advocate

9:10 AM **Panel Session: Disparities in Clinical Pain Management**
Moderator: Eliseo Peréz-Stable, M.D., Director, National Institute on Minority Health and Health Disparities

9:20 AM **Overview: Differences in Opioid Prescribing by Specialty and Demographics**
Asheley Cockrell Skinner, Ph.D., Duke University

9:50 AM **Understanding Adverse Selection: The Role of Mental Health in Opioid Therapy for Chronic Pain**
Mark Sullivan, M.D., Ph.D., University of Washington, Seattle

10:10 AM Poster Session and Break

10:40 AM **Using Interactive Virtual Humans to Improve Pain Care for Racial Minority and Low-income Patients**
Adam T. Hirsh, Ph.D., Indiana University-Purdue University, Indianapolis

11:00 AM **Insights into Ethnic Differences in Pain from Experimental Studies**
Claudia Campbell, Ph.D., Johns Hopkins University

11:20 AM **Panel Session Q & A**

11:40 AM **Closing Remarks**
Martha Somerman, D.D.S., Ph.D., Director, National Institute of Dental and Craniofacial Research

12:00 PM Adjourn

Appendix 2: Meeting Participants

Executive Committee

Walter Koroshetz (Chair), Director, National Institute of Neurological Disorders and Stroke
David Shurtleff, Acting Director, National Center for Complementary and Integrative Health
Patricia Grady, 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

Vice Admiral Jerome Adams, M.D., M.P.H.
U.S. Surgeon General

Ishmail Abdus-Saboor, Ph.D.
Postdoctoral Fellow, University of Pennsylvania

Claudia Campbell, Ph.D.
Associate Professor, Johns Hopkins University

George Carter
Administrator, Sickle Cell Chapters of Virginia, Inc.

Asheley Cockrell Skinner, Ph.D.
Associate Professor, Duke University

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

Lee Fisher, Ph.D.
Assistant Professor, University of Pittsburgh

Patricia Grady, Ph.D., R.N., FAAN
Director, National Institute of Nursing Research

Adam T. Hirsh, Ph.D.
Associate Professor, Indiana University-Purdue University, Indianapolis

Walter Koroshetz, MD
Director, National Institute of Neurological Disorders and Stroke; Chair, NIH Pain Consortium Executive Committee

William Maixner, D.D.S., Ph.D.
Professor, Duke University

Jose Moron-Concepcion, Ph.D.
Associate Professor, Washington University

Anne Z. Murphy, Ph.D.
Professor, Georgia State University

Ann O'Mara, Ph.D., R.N., FAAN
Program Director, National Cancer Institute

Judith Paice, R.N., Ph.D.
Director, Cancer Pain Program, Northwestern University; Feinberg School of Medicine

Eliseo Peréz-Stable, M.D.
Director, National Institute on Minority Health and Health Disparities

Michaela Prochazkova, Ph.D.
Research Fellow, National Institute of Dental and Craniofacial Research

Khara Ramos, Ph.D.
Senior Science Policy Analyst, National Institute of Neurological Disorders and Stroke

Brian L. Schmidt, D.D.S., M.D., Ph.D.
Director, New York University College of Dentistry

David Shurtleff, Ph.D.
Acting Director, National Center for Complementary and Integrative Health

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

Sarah Stanley, MBBCh, Ph.D.
Associate Professor, Mount Sinai Medical Center

Mark Sullivan, M.D., Ph.D.
Professor, University of Washington, Seattle

Norman Taylor, M.D., Ph.D.
Assistant Professor of Anesthesia, Massachusetts General Hospital

Rita Valentino, Ph.D.
Director, DNB, National Institute on Drug Abuse

Nora Volkow, M.D.
Director, National Institute on Drug Abuse

NIH Pain Consortium Members

National Cancer Institute
National Eye Institute
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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