
# Advancing Therapeutic Development for Pain and Opioid Use Disorders Through Public-Private Partnerships: Proceedings of a Workshop



## DETAILS

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# Advancing Therapeutic Development for Pain and Opioid Use Disorders Through Public–Private Partnerships

## PROCEEDINGS OF A WORKSHOP

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*Rapporteurs*

Forum on Neuroscience and
Nervous System Disorders

Board on Health Sciences Policy

Health and Medicine Division

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We thank the following individuals for their review of this proceedings:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by **SARA ROSENBAUM,** The George Washington University, and **BRADFORD H. GRAY,** The Urban Institute. They were responsible for making certain that an independent examination of this proceedings was carried out in accordance with

standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteurs and the National Academies.

# Contents

# 1

# Introduction and Background[1]

Chronic pain is one of the most prevalent, costly, and disabling health conditions in the United States. Estimates show that more than 11 percent of the American population suffer from chronic pain (Nahin, 2015), yet the federal pain research investment has been minimal, said Christin Veasley, co-founder and director of the Chronic Pain Research Alliance.

In parallel with a gradual increased recognition of the problems of treating chronic pain, the opioid epidemic has emerged as a growing public health emergency. According to the Centers for Disease Control and Prevention (CDC), opioid overdoses account for 115 American deaths each day,[2] contributing to the dramatic increase in overall drug overdose deaths since 1999 (see Figure 1-1). In 2016, at least 46 overdose deaths involved prescription opioids each day (Hedegaard et al., 2016). The intersection of these two crises lies in the fact that an unintended consequence of treating pain has been an increasing number of opioid prescriptions and diversion of drugs for illicit purposes, said Story Landis, vice chair of the National Academies' Forum on Neuroscience and Nervous System Disorders and former director of the National Institute of Neurological Disorders and Stroke (NINDS). Sharon Walsh, professor of behavioral science, psychiatry,

[1]The planning committee's role was limited to planning the workshop, and the Proceedings of a Workshop was prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They should not be construed as reflecting any group consensus.

[2]For more information, go to https://www.cdc.gov/drugoverdose/epidemic/index.html (accessed December 27, 2017).

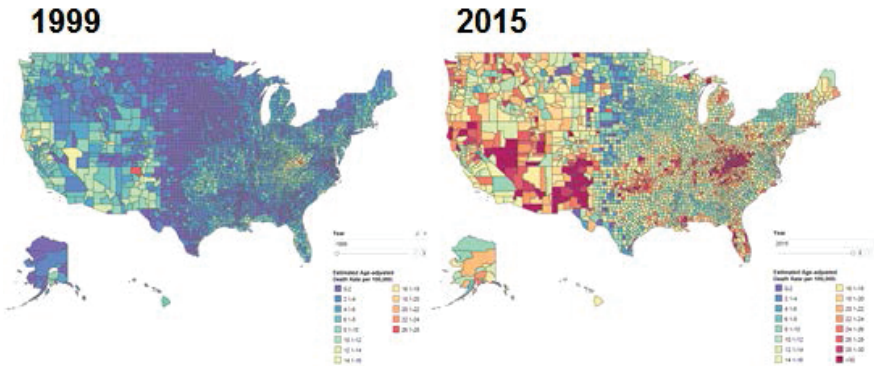


**FIGURE 1-1** Drug overdose death rates**.** Very high death rates from all drug overdoses were seen in only two relatively small regions in 1999, but by 2015, overdose death rates had spiked over nearly all of the United States. In 2015, new color categories were added to the map for areas where death rates exceeded 28 per 100,000.
SOURCES: Presented by Nora Volkow, October 11, 2017. Center for Disease Control and Prevention/National Center for Health Statistics, National Vital Statistics System; designed by L. Rossen, B. Bastian, and Y. Chong.

pharmacology, and pharmaceutical sciences at the University of Kentucky, added that patients with chronic pain and patients with opioid use disorders have much in common. Both populations are stigmatized, and because their providers may also be stigmatized, even adequate treatment may be difficult to obtain, she said. Moreover, both disorders are misunderstood, and health professionals lack the tools needed for proper diagnosis and treatment, said Walsh.

One intervention or strategy by itself will not resolve the opioid crisis, said Nora Volkow, director of the National Institute on Drug Abuse. Developing non-addictive pain medications will, however, address the needs of patients with severe pain and reduce the likelihood that they will become addicted to opioids, she added. In parallel, treatments are needed for those who become addicted, and interventions are needed to prevent or reverse overdosing, said Volkow. She suggested that being in the midst of this crisis may motivate companies and academic institutions to move with greater urgency toward addressing the roadblocks to progress.

In May 2017, Francis Collins, director of the National Institutes of Health (NIH), and Volkow announced a public–private partnership to develop solutions to the opioid crisis and cut in half the time it takes to develop non-addictive analgesics (Volkow and Collins, 2017). Walter Koroshetz, director of NINDS, noted that following this announcement, Collins convened government agencies and researchers from industry and academia for a series of three meetings, focusing on (1) medications development for opioid use disorders and for overdose prevention and reversal; (2) development of safe, effective, non-addictive pain treatments; and (3) understanding the neurobiological mechanisms of pain. To advance the planning of NIH's anticipated public–private partnerships, the National Academies' Forum on Neuroscience and Nervous Systems Disorders hosted this public workshop that brought together a diverse group of stakeholders from academia, federal agencies, advocacy organizations and companies developing therapeutics for pain and opioid use disorders (see Box 1-1).

**BOX 1-1**
**Statement of Task**

An ad hoc committee will plan and conduct a 1.5-day public workshop that will bring together key stakeholders from government, academia, industry, and disease-focused organizations to explore opportunities for public–private partnerships to advance the development of novel treatments for pain and opioid use disorder.

- Review the state of the science for opioid and non-addictive pain treatments.
  - Provide an overview of emerging pain models, including those in the peripheral nervous system (e.g., induced pluripotent stem cells and human experimental biology).
  - Discuss the progress on the identification and validation of targets and biomarkers (neuroinflammation, genetic, proteomics, etc.). Explore whether there is a systematic methodology to validating biomarkers to determine their usefulness.
  - Examine approaches to testing new formulations and drugs and discuss the patient populations needed for those clinical trials.
  - Consider the formulation of promising pain medications—beyond opioid analgesics—that may have been shelved by companies.
- Explore opportunities and challenges to changing the formulation of marketed prescription opioids to decrease misuse, addiction, and potential overdoses (e.g., different delivery systems and antitampering mechanisms).
- Consider regulatory issues related to the approval of pain medications and discuss potential opportunities to address those challenges.
- Discuss public–private partnerships that might facilitate and de-risk the development of drugs to treat opioid overdoses and non-addictive therapeutics

for pain (e.g., an Accelerating Medicines Partnership for pain). Highlight lessons learned from industry and opportunities to advance the development of these drugs (e.g., a designated clinical trial network for pain).

The committee will develop the agenda for the workshop, select and invite speakers and discussants, and moderate the discussions. Proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

## WORKSHOP OBJECTIVES

The purpose of the workshop, Koroshetz explained, was to discuss potential strategies to accelerate development of non-addictive pain medications and treatments for opioid use disorders. He reported that NIH and other federal and industry partners are working to create public–private partnerships to address the dual problems of treating pain and preventing and treating opioid addiction and overdose. The workshop was intended to explore the relative value of potential projects and think about how these projects could be operationalized to ensure that the science is advanced and that industry partners get what they need in order to move research and development forward. Topics discussed at the workshop aligned with the priorities identified by the Federal Pain Research Strategy (FPRS).

While recognizing the value of non-pharmacological approaches to pain management, the workshop focused on developing medications. Other important issues that are out of scope for the workshop and this report include pain education and workforce issues.

## THE PUBLIC HEALTH IMPACT OF PAIN AND OPIOID USE DISORDERS

Opioid medications can be very effective for the treatment of acute pain, yet they are also highly rewarding and addictive, said Volkow. In addition, opioids are not very effective for chronic pain because tolerance develops, and as a result, people take higher doses, increasing the risk of addiction, she added. Overprescribing of opioids contributed to the diversion of these drugs to the black market. After stricter clinical guidelines were introduced and education increased, the number of prescription opioids decreased, and some those who were already addicted to the prescription opioids transitioned to heroin, which was cheaper and, in many

instances more accessible, said Volkow. This incentivized the black market, and imports of very pure heroin markedly increased in the United States, fueling the heroin epidemic, and accelerating the number of deaths due to heroin overdoses, she added. More recently, synthetic opioids such as fentanyl, which is 50 more potent than heroin, have flooded the market either laced with heroin or prescription opioids, and in some instances by itself. Volkow said that while it is not known whether the combination of fentanyl and heroin is more lethal than either drug alone, fentanyl overdoses are much harder to reverse than those from heroin (CDC, 2013; Schumann et al., 2008).

The number of lives lost to drug overdoses has climbed dramatically in recent years, from 114 per day in 2013 to 144 per day in 2015 (Rudd et al., 2016), said Jessica Hulsey Nickel, president and chief executive officer of the Addiction Policy Forum. According to the CDC, overdose deaths involving opioids in 206 were five times higher than in 1999 (2017). A recent study found that opioid overdoses have reduced life expectancy in the United States by 2 months (Dowell et al., 2017). Shame, guilt, and embarrassment cause this illness to become a dark family secret, said Nickel, and the lack of treatment options precipitates long-term effects on affected individuals and their families. The disparity between how opioid use disorder is treated compared with other illnesses perpetuates the crisis. Nickel recounted a statement made by a mother whose two sons died of drug overdoses, "Had they suffered from diabetes or skin cancer, they would have been provided the medical care and attention necessary to live a full life."

## SELECTED FEDERAL INITIATIVES TO ADDRESS THE CHALLENGE OF TREATING PAIN AND OPIOID USE DISORDERS AND RELATED NATIONAL ACADEMIES' REPORTS

A provision in the Patient Protection and Affordable Care Act (ACA) required the Secretary of Health and Human Services to create the Interagency Pain Research Coordinating Committee (IPRCC),[3] with representation from all federal agencies as well as the public, according to Linda Porter, director of the Office of Pain Policy at NINDS. A second requirement of ACA was a report by the National Academies on pain in America,

[3]For more information, go to https://iprcc.nih.gov/ (accessed December 27, 2017).

which was published in 2011 (IOM, 2011) (see Box 1-2). At the request of the U.S. Food and Drug Administration (FDA), the National Academies published a consensus study report in 2017 (see Box 1-3) with recommendations on actions that the FDA and other organizations should take to address the opioid use epidemic (NASEM, 2017).

In conjunction with these efforts, CDC released guidelines for prescribing opioids for chronic pain in 2016.

A consequence of the 2011 IOM report was the strong suggestion for a federal pain strategy. IPRCC, in conjunction with the NIH Office of Pain Policy, released the Federal Pain Research Strategy (FPRS) in November 2017—the same month the President's Commission on Combating Drug Addiction and the Opioid Crisis published its final report. This strategy encompasses both basic and clinical science efforts across the full continuum of pain, from prevention and management of acute pain, the transition from acute to chronic pain, and the management of chronic pain, said Porter.

**BOX 1-2**
**Recommendations from the IOM Report**
***Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research* Relevant to This Workshop**
**(IOM, 2011)**

- Improve the collection and reporting of data on pain.
- Create a comprehensive population health-level strategy for pain prevention, treatment, management, and research.
- Promote and enable self-management of pain.
- Develop strategies for reducing barriers to pain care.
- Support collaboration between pain specialists and primary care clinicians, including referral to pain centers when appropriate.
- Revise reimbursement policies to foster coordinated and evidence-based pain care.
- Provide consistent and complete pain assessments.
- Designate a lead institute at the National Institutes of Health responsible for moving pain research forward, and increase the support for and scope of the Pain Consortium.
- Improve the process for developing new agents for pain control.
- Increase support for interdisciplinary research in pain.
- Increase the conduct of longitudinal research in pain.

**BOX 1-3**
**Recommendations from the National Academies Consensus Study Report *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use* Relevant to This Workshop (NASEM, 2017)**

- Invest in research to better understand pain and opioid use disorder.
- Consider potential effects on illicit markets of policies and programs for prescription opioids.
- Improve reporting of data on pain and opioid use disorder.
- Invest in data and research to better characterize the opioid epidemic.
- Incorporate public health considerations into opioid-related regulatory decisions.
- Require additional studies and the collection and analysis of data needed for a thorough assessment of broad public health considerations.
- Ensure that public health considerations are incorporated adequately into clinical development.
- Increase the transparency of regulatory decisions for opioids in light of the committee's proposed systems approach.
- Strengthen the post approval oversight of opioids.
- Conduct a full review of currently marketed/approved opioids.
- Improve access to drug take-back programs.
- Facilitate reimbursement for comprehensive pain management.
- Improve the use of prescription drug monitoring program data for surveillance and intervention.
- Evaluate the impact of patient and public education about opioids on promoting safe and effective pain management.
- Expand treatment for opioid use disorder.
- Remove barriers to coverage of approved medications for treatment of opioid use disorder.
- Leverage prescribers and pharmacists to help address opioid use disorder.
- Improve access to naloxone and safe injection equipment.

## The Federal Pain Research Strategy

The FPRS was set up under the ACA and includes recommendations made to the Secretary of Health and Human Services to ensure that NIH and other federal agencies are not duplicating efforts. IPRCC maintains a database of funding programs across all federal agencies, including NIH, the Departments of Veterans Affairs and Defense, the FDA, the CDC, and the Agency for Healthcare Research and Quality. Porter noted that through a series of crosscutting workgroup meetings, a list of priorities emerged

for the FPRS, namely to identify opportunities for therapeutic development of non-addictive pain medicines and to address clinical challenges and immediate needs for developing pain therapeutics (see Box 1-4 for a list of select top priorities). Porter said that an aim of the FPRS is to complete the National Pain Strategy, a broad-ranging federal effort to change how pain is managed, educate professionals, and raise public awareness, which follows the recommendations of the 2011 IOM report on pain (IOM, 2011).

She also mentioned a Common Fund proposal in development for a project that will involve scientists from diverse areas of research and employ many advanced technologies to identify acute to chronic pain signatures. Common Fund projects are supported with set-aside funds that NIH uses for projects that are too big and too disorder-neutral for any single agency to support, said Porter.

**BOX 1-4**
**Select Top Priorities in the Federal Pain Research Strategy (NIH, 2017)**
**Presented by Linda Porter**

- Develop safer opioids, new, non-opioid analgesics, and the first generation of disease-modifying agents.
- Develop a research network.
- Develop, evaluate, and improve models of pain care.
- Develop approaches incorporating principles of precision medicine to prevent and effectively treat chronic pain.
- Conduct prospective studies for susceptibility and resilience factors underlying the transition from acute to chronic pain.
- Understand and address plasticity mechanisms that promote persistent pain and (endogenous) resolution mechanisms that may reverse persistent pain.
- Conduct mechanistic trials of risk and resilience to chronic pain with meaningful outcome measures.
- Determine the mechanisms that sustain or resolve chronic pain and which of these elements can be intrinsically and extrinsically modulated.
- Determine optimal safe and effective chronic pain management.
- Determine optimal approaches for use of self-management strategies in chronic pain.
- Determine the bidirectional relationship between common co-morbidities and chronic pain.
- Understand mechanisms of childhood chronic pain.
- Investigate biological, psychological, and social mechanisms that underlie development and persistence of chronic pain in disparate populations.

### Non-Pharmacological Approaches to Treating Pain

David Shurtleff, acting director of the National Center for Complementary and Integrative Health (NCCIH), added that while medications clearly play a role in treating opioid use disorders—with many tools already in the armamentarium, including methadone, buprenorphine, naltrexone, and Narcan®—behavior therapies are needed to give people the tools they need to cope with their cravings, addictions, and relapses. Cognitive-behavioral therapies and mindfulness-based approaches teach people new strategies to manage their disorders. He noted that these non-pharmacologic therapies, could also address pain and other co-morbidities such as depression, anxiety, and posttraumatic stress disorder, which are common in people with opioid use disorders. NIH has programs in place to move both non-pharmacologic and natural product approaches forward, including the Stimulating Peripheral Activity to Relieve Conditions (SPARC)[4] program; projects exploring brain circuitry and neuromodulation as part of the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative[5]; and the natural products portfolio at NCCIH, said Shurtleff.

Expanding research on non-pharmacological therapies for pain, including behavioral modification, cognitive therapy, and neuromodulation, would broaden the scope of a public–private partnership to address the chronic pain and opioid epidemic, said Porter and Volkow.

## ORGANIZATION OF PROCEEDINGS

The following proceedings summarize the workshop presentations and discussions. This chapter provides background for the motivation for the workshop and an overview of the opioid epidemic, including related federal initiatives to address it. Chapter 2 opens with the patient perspective on living with pain and includes a summary of challenges that have slowed development of adequate treatments for pain and opioid use disorders. Chapter 3 provides a brief overview of the state of the science on opioid and non-addictive pain medications, including the latest research

[4]For more information, go to https://commonfund.nih.gov/sparc (accessed December 27, 2017).

[5]For more information, go to https://www.braininitiative.nih.gov (accessed December 27, 2017).

on the molecular physiology and genetics of pain, as well as on preclinical models for pain therapy development. Chapter 4 focuses on clinical efforts to develop non-addictive pain medications, including biomarker-based drug discovery, research underway to prevent the acute-to-chronic pain transition, and a discussion of regulatory issues related to the approval of pain medications. Chapter 5 shifts focus to the development of treatments for opioid use disorders and reversing overdose. Chapter 6 concludes with discussions about existing and proposed partnerships and the role of payers in developing treatments for pain and opioid use disorders.

# 2

# Exploring Challenges to Developing Treatments for Pain and Opioid Use Disorders

Given the complexity of chronic pain and opioid use disorders, many workshop participants discussed challenges to advancing the discovery and development of new treatments, including the complex experience of pain, a lack of resources to treat pain, insufficient understanding of pain mechanisms, and limitations in conducting clinical trials.

## THE COMPLEX EXPERIENCE OF PAIN

Christin Veasley reminded workshop participants that everyone who lives with chronic pain experiences it differently. Moreover, she said, although a survey by Research!America Analytics found that about two-thirds of respondents said they know someone who experiences "pain so severe that they sought prescription medications to treat it," only 18 percent described pain as a major public health problem (Research!America, 2013). She also said there is a disconnect between how the public views and defines pain and chronic pain compared to the perspectives of researchers and clinicians.

The experience of chronic pain is very complex, said Veasley. Many people with chronic pain have multiple diagnoses that contribute to their experience of pain, yet these classifications and diagnoses may lack meaningfulness to patients who simply say they have chronic pain. In addition, people experience pain differently from a biopsychosocial perspective, she said. So, for instance, while one person with fibromyalgia may have fatigue and impaired psychosocial function, another may have a sleep disorder, depression, and dyscognition. These co-occurring symptoms combine to create a unique experience for each individual, said Veasley. Nora

Volkow added that pain is variable over time, with some syndromes having exacerbation of pain later in the day. This could be explained by social processes such as less activity and distraction at the end of the day so that without the distractors patients are more aware of the pain sensation, but this also could reflect circadian variability, she said.

Stigma and personal biases also influence how the public views people with pain, said Veasley. Due to recent awareness efforts, families, friends, and workplaces find it acceptable for someone to have a diagnosed chronic pain disorder, however, due to the continued stigmatization surrounding pain, many still consider it a "weakness" if the person allows the pain condition to impact his/her productivity and ability to function in various professional and social roles. Also related to stigmatization is the criminalization of pain, where people suffering from chronic pain are perceived as criminals or encounter increased scrutiny because of their pain management treatments (Terplan, 2017). Having chronic pain does not mean that you are an opioid user, and being an opioid user does not mean you are an opioid abuser who would engage in illegal activities to access the drug, said Veasley. Even those who have an opioid use disorder deserve the best, most humane, and empathic medical care, she said.

## INSUFFICIENT RESOURCES TO TREAT PAIN

From a clinical perspective, Veasley noted a shortage of pain specialists, insufficient training about pain for primary care providers, no team-based multimodal coordinated treatment, and a meager evidence base on which to assess benefits and risks of any treatment approach. Sharon Walsh added that there are barriers to using drugs currently available. For example, prior authorization may be needed before buprenorphine can be given at discharge from the emergency department. She also cited the need for higher affinity and efficacy therapies for both overdose and maintenance, particularly in light of the availability of fentanyl and fentanyl analogues, as well as a need for better data about who is at risk of repeat overdose. Scott Powers, professor of pediatrics at the University of Cincinnati College of Medicine, noted that the discovery and development of novel treatment approaches will also require a better understanding of reasons for adherence and non-adherence, and strategies to maximize adherence. William Maixner, director of the Center for Translational Pain

Medicine at Duke University, added that reimbursement is poor for multidisciplinary services, biopsychosocial approaches, and non-opioid-based approaches to treat pain.

Volkow suggested that combinations of medications may be needed to make a meaningful difference in the lives of people with chronic pain, opioid use disorders, and complex co-morbidities, yet the regulatory approval process for combinations of drugs can be particularly daunting.

## INSUFFICIENT UNDERSTANDING OF PAIN MECHANISMS

To achieve the Federal Pain Research Strategy priority of identifying new, non-addictive pain therapies and treatments for opioid use disorders, Porter noted that a deeper understanding of pain mechanisms will be needed. Pain is a highly heterogeneous, multisystem illness that involves the neurologic, endocrine, and immune systems, yet few animal or human models account for this complexity and heterogeneity, said Veasley. In complex diseases such as pain, thousands of genetic modifiers influence risk, noted Clifford Woolf, professor of neurology and neurobiology at Harvard Medical School and director of the F.M. Kirby Neurobiology Center at Children's Hospital Boston. Genes may also modulate the transition from acute to chronic pain, said Volkow. Other neural mechanisms that underlie the acute-to-chronic pain transition are also not well understood, said Maixner. Woolf added that most preclinical models are built around evoked pain rather than spontaneous pain, although the latter is the most common complaint of patients. Tony Yaksh, professor of anesthesiology and pharmacology at the University of California, San Diego, and John Kehne, program director in the Division of Translational Research at the National Institute of Neurological Disorders and Stroke, both said that preclinical research in pain, as in many other disease areas, has been plagued by a lack of reproducibility.

## UNDERSTANDING CHALLENGES IN CONDUCTING CLINICAL TRIALS

Elevated placebo responses in pain trials have made it difficult to demonstrate efficacy in clinical trials, said Tor Wager, director of the Cognitive and Affective Neuroscience Laboratory at the University of Colorado Boulder. He commented that the biological, genetic, and

neurocircuitry mechanisms underlying the placebo response are complex, poorly understood, and entangled with many emotional, experiential, cultural, and cognitive factors. Andrew Ahn, chief scientific officer for pain and headache at Eli Lilly and Company, added that placebo responses may also be affected by the natural history of the disorder (e.g., the frequency of pain attacks) and expectations about the treatment. Wager stated that statistical artifacts further compromise understanding of placebo responses.

Clinical trials have also been hampered by inadequate measures of pain that incorporate sleep and mood, fatigue, and function, said Veasley. Seena Ajit, assistant professor of pharmacology and physiology at Drexel University, added that the role of circadian variability in pain responses has not been studied from the perspective of different biomarkers of pain, including neuroimaging and miRNA markers.

Conducting efficient clinical trials has also been limited by implementation barriers. Ahn noted that pain is generally treated by primary care physicians, whose practices are not set up to allow comprehensive assessment of the problem or to deliver much-needed multidisciplinary care. Walsh added that few providers and Federally Qualified Health Centers offer treatment for opioid use disorders.

Yaksh and Walter Koroshetz said that progress in clinical trials has also been slowed by inadequate sharing of data and knowledge about preclinical and clinical pain therapy development, and the science of addiction. Furthermore, Jessica Nickel noted that because there is inadequate reimbursement for drugs that treat addiction or reverse overdose, pharmaceutical companies lack incentives to develop these treatments.

## THE PENDULUM SWING OF CARE: UNDERSTANDING PATIENT NEEDS

Veasley said there has been a pendulum swing in the medical scientific world when it comes to managing pain (see Figure 2-1). On one extreme of the pendulum, no one is prescribed opioids, there is a basic science research focus, biologic measures with little to no self-report are used, and patients are not involved in the research process. On the other extreme of the pendulum, opioids are used more frequently, and translational and clinical science research has increased, with a focus on objective biological measures as well as patient-reported outcomes. Placebo-controlled trials are being supplemented with pragmatic real-world trials, and patients have

become an integral component of the research enterprise. The challenge is finding a balance between the two extremes and what's best for the patient, Veasley said.

Potential opportunities presented by individual workshop participants to address these challenges are highlighted in succeeding chapters.

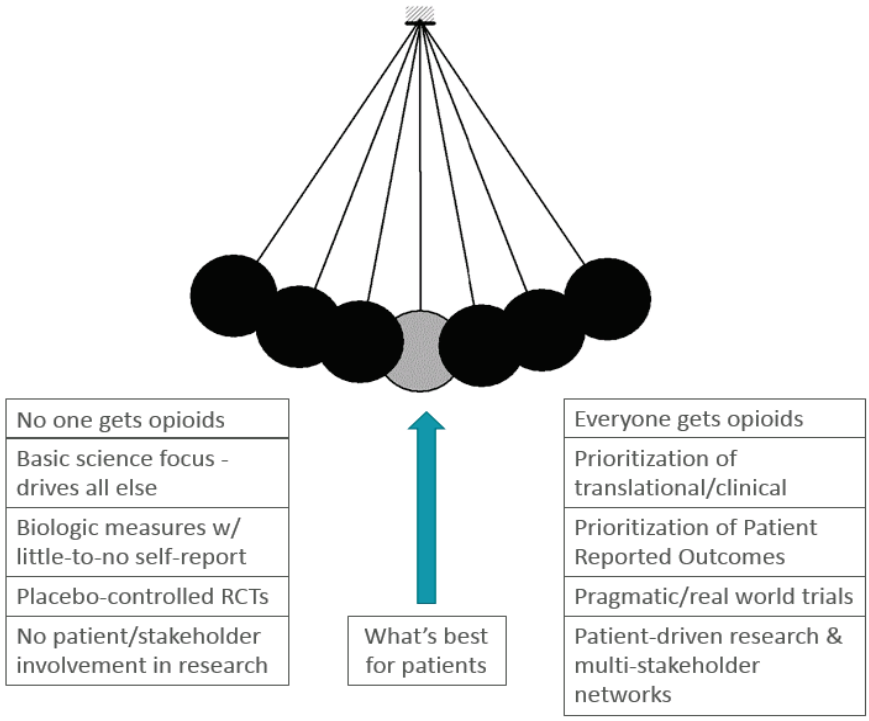


**FIGURE 2-1** Pendulum swing in the medical scientific world: Pain treatment, research, drug development, and the involvement of patients in decision making has swung dramatically in recent years. What is best for patients probably rests somewhere in the middle.
NOTE: RCT = randomized controlled trial.
SOURCE: Presented by Christin Veasley, October 11, 2017.

# 3

# Exploring the State of the Science and Preclinical Models for Pain Therapeutic Development

**Highlights**

- Pain is mediated by complex circuitry, neuronal and non-neuronal cells, synapses, sodium channels, and inflammatory mediators (Yaksh).
- Common neural circuits are involved in pain, addiction, and depression (Volkow).
- While neuron transmission in acute pain is relatively known, greater understanding of the molecular physiology of chronic pain is needed (Diatchenko).
- Genetic studies have revealed many potential targets for pain therapies, including sodium channels, epidermal growth factor receptor, β-adrenergic receptor, and isoforms of the μ-opioid receptor (Diatchenko, Maixner).
- Genetics has demonstrated that there may be multiple molecular pathways to a single pain syndrome (Diatchenko).
- Translating genetically identified targets into therapies and biomarkers involves multiple steps, moving from association studies to preclinical models to clinical studies (Diatchenko).
- Induced pluripotent stem cells from patients can be used to model diseases in vitro, explore mechanisms of pain, develop high-throughput screening tools, identify who is at risk for transitioning from acute to chronic pain, and design new therapeutics (Woolf).
- Applying new technologies to study brain circuits and neural activity, such as those developed as part of the BRAIN Initiative (e.g., optogenetics), might lead to a better understanding of how neural activity and pain circuits are disrupted to cause pain (Gereau).
- Companion animals provide potentially useful preclinical models, particularly for pain conditions that occur naturally in those animals, such as osteoarthritis and bone cancer in dogs (Brown).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Given the complexity of pain, several workshop participants highlighted the need for a greater understanding of the underlying mechanisms of pain. Throughout the workshop, individual participants explored the known cellular and molecular mediators of pain and considered opportunities in the preclinical space that might advance therapeutic development.

## NEURAL CIRCUITS, CELLS, AND MOLECULAR MEDIATORS OF PAIN

There have been great advances in understanding pain from a systems and circuitry perspective, as well as the physiology and cell biology of central and peripheral systems mediating pain sensation and behavior, said Tony Yaksh. This understanding now includes the recognition that pain processing involves complex circuitry as well as the involvement of neuronal and non-neuronal cells, synapses, sodium channels, and inflammatory mediators (Woller et al., 2017). Moreover, there is a commonality in some of the neural circuits involved in pain and addiction, as well as in depression, said Nora Volkow. Indeed, patients with substance use disorders are at much greater risk of suffering from chronic pain, and patients with chronic pain are at greater risk of suffering from depression, she added. What that means is that targeting this shared neurocircuitry may have wider benefits than would be had simply by targeting the μ-opioid or the type 3 dopamine receptor, said Volkow.

Although neuron transmission in acute pain is relatively well understood, the molecular physiology of chronic pain remains less clear, said Luda Diatchenko, professor and Canada Excellence Research Chair in Human Pain Genetics at McGill University. Only recently have scientists begun to understand the genetics of pain, she said. From studies of very rare monogenic pain disorders, the first gene linked to pain—the gene for the neurotrophin nerve growth factor (NGF)—was identified about 20 years ago (Indo et al., 1996). Diatchenko said that understanding the mechanisms by which NGF enhances pain led to the identification of two major drug targets, NGF itself and its cognate receptor—the tropomyosin-related kinase A receptor (TrkA) (Mantyh et al., 2011). More recently, mutations in the sodium channel gene SCN9A were found to be responsible for more than half of all cases of congenital insensitivity to pain (Drenth and Waxman, 2007). Diatchenko said that more than six pharmaceutical companies have compounds targeting the sodium channel in development.

Today, thanks to genetic linkage analysis and association studies, dozens of genes have been associated with various pain conditions (Zorina-Lichtenwalter et al., 2016) (see Figure 3-1).

| Gene | # of citations |
|---|---|
| *COMT* | 16 |
| *HTR2A* | 7 |
| *ESR1* | 4 |
| *ADRB2* | 3 |
| *IL1A* | 3 |
| *OPRM1* | 3 |
| *SLC6A4* | 3 |
| Other | 13 |

| Gene | # of citations |
|---|---|
| *MTHFR* | 15 |
| *ACE* | 6 |
| *PRDM16* | 6 |
| *TNF* | 6 |
| *ESR1* | 5 |
| *AJAP1* | 4 |
| *C7orf10* | 4 |
| *DBH* | 4 |
| *FHL5* | 4 |
| *LRP1* | 4 |
| *LTA* | 4 |
| *MMP16* | 4 |
| *TRPM8* | 4 |
| Other | 46 |

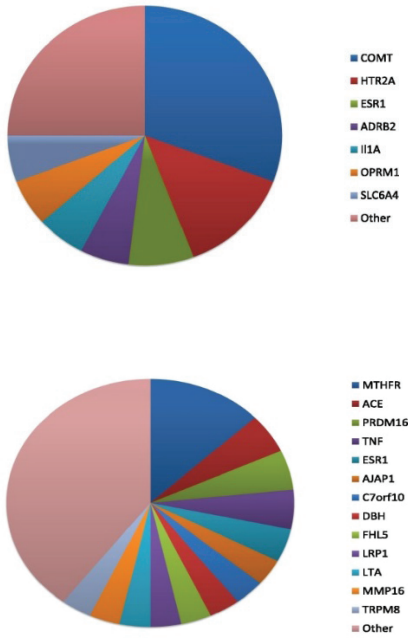


**FIGURE 3-1** Genetic loci associated with musculoskeletal pain (top chart) and migraine (bottom chart), quantified by the number of genetic association studies.
NOTE: ACE = angiotensin I converting enzyme; ADRB2 = beta-2 adrenergic receptor; AJAP1 = adherens junctions-associated protein 1; C7orf10 = succinyl-CoA:glutarate-CoA transferase; COMT = catechol-O-methyl transferase; DBH = dopamine beta-hydroxylase; ESR1 = estrogen receptor 1; FHL5 = four-and-a-half LIM domains 5; GCH1 = GTP cyclohydrolase; HTR2A = 5-hydroxytryptamine (serotonin) receptor 2A; LRP1 = low density lipoprotein receptor related protein 1; LTA = lymphotoxin alpha; MMP16 = matrix metalloproteinase 16; MTHFR = methelynetetrahydrofolate reductase; OPRM1 = mu-1 opioid receptor; PRDM16 = PR domain-containing 16; SLC6A4 = solute carrier family 6 (serotonin transporter); TNF = tumor necrosis factor; TRPM8 = transient receptor potential cation channel, subfamily M, member 8 (menthol and cold receptor).
SOURCES: Presented by Luda Diatchenko, October 12, 2017; Zorina-Lichtenwalter et al., 2016.

More genome-wide analysis studies (GWASs) are coming, said Diatchenko. Her lab has put together a searchable database called the Human Pain Genes Database (HPGDB) to summarize information about each single positive association result as a tool to be used for drug development.

William Maixner, suggested that genetic studies are enabling what he called "reverse translation," in which identification of genes linked to disease lead to the identification of targets. Using molecular signatures identified in a series of cohort studies, he and his colleagues have identified three novel targets: epidermal growth factor receptor (EGFR) (Martin et al., 2017), β-adrenergic receptor (Martin et al., 2015), and the six transmembrane helix isoform of the μ-opioid receptor (6TM-mOR) (Shabalina et al., 2009). There are now chemical entities in development, ready to move from preclinical to clinical studies, he said.

## PRECLINICAL EFFORTS TO IDENTIFY PAIN TARGETS AND TREAT PAIN

To gain a better understanding of what is needed for the development of safe, effective, and non-addictive pain treatments, many workshop participants discussed novel methods for identifying targets for pain and considered what might be done to improve target validation.

### Genetic Approaches for Target Identification and Translation

The discovery of genetic variants that are associated with any medical condition provides novel biological insight and potential therapeutic targets and biomarkers, which can be used to advance the development of new treatments, including personalized medicine, said Diatchenko. Translating those discoveries into new drugs involves several steps, moving from association studies, to understanding the molecular genetic mechanisms of functional variants, to animal studies demonstrating how the genetic variant contributes to pain in vivo, and finally to clinical trials. Diatchenko used the metaphor of a "translational clock" to illustrate how her team "ticked" through these steps on the way to developing a treatment for facial pain. They first showed that variants of the gene encoding catecholamine-O-methyltransferase (COMT) were associated with pain sensitivity and the risk of developing facial pain (Diatchenko et al., 2005). Next, they identified the molecular mechanism via the alternation of the secondary structure of RNA responsible for this phenomenon (Nackley et al.,

2006). Following this, they showed in animal models that pain sensitivity is increased by inhibiting COMT via the activation of beta adrenergic receptors (Nackley et al., 2007), and finally they conducted a clinical trial, which showed that propranolol, a non-selective beta-blocker, was effective in treating facial pain in the manner dependent of COMT genotype (Tchivileva et al., 2010). Using a similar approach, they have demonstrated that inhibition of EGFR with compounds already on the market blocks pain in mice (Martin et al., 2017). Diatchenko noted that both of these approaches use repurposed drugs, and that neither of these classes of drugs have a potential for abuse.

Genetics has also shown that there may be multiple molecular pathways leading to a single pain syndrome such as migraine (Freilinger et al., 2012), said Diatchenko. What that means, she said, is that even in a population subgroup there may be heterogeneity in response to a certain treatment. Moreover, genetic variants and pathways that contribute to chronic pain are not necessarily organ specific, but may be involved in many different types of pain, she added. Instead of planning treatment regimens based on the type or site of pain, it may be more effective to use molecular profiling of individuals to identify therapeutic targets (see Figure 3-2). This will require a lot more GWAS, she said, and can only be done through the collaboration of geneticists working across different pain fields.

### Disease Modeling in Human Cells, Tissue, and Organoids

Clifford Woolf, professor of neurology and neurobiology at Harvard Medical School and director of the F.M. Kirby Neurobiology Center at Children's Hospital Boston, proposed using stem cell-derived neurons for the following purposes: investigating known targets, conducting target-based drug screens, disease modeling to identify mechanistic drivers of pain, identifying individuals at risk of transitioning from acute to chronic pain, conducting phenotypic drug screens, aiding in personalized treatment selection, and conducting in vitro clinical trials. This is possible, he said, by combining stem cell technology with CRISPR[1] engineering technology,

[1]Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is a new, cheap, quick, and easy-to-use gene-editing technique that allows investigators to alter the DNA of nearly any cell or organism.

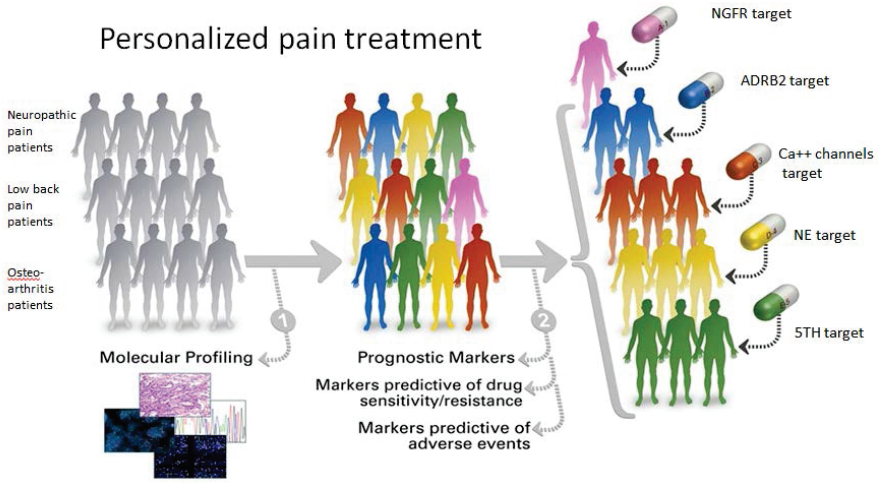


**FIGURE 3-2** Non-organ-specific approach to treating pain**.** Rather than prescribing pain medications based on the type or site of pain, it may be possible through molecular profiling to identify markers predictive of sensitivity to drugs against different targets.
SOURCE: Presented by Luda Diatchenko, October 12, 2017.

which allows investigators to generate induced pluripotent stem cells (iPSCs) from the fibroblasts of patients with a certain phenotype, characterize neurons grown in culture from those iPSCs, replicate mutations identified in the patient material, and engineer mice to have those same mutations.

For example, his lab has used this approach to interrogate nociceptor or nociceptor-like cells that have high expression of the voltage-gated sodium channel Nav 1.7. Nociceptors are peripheral neurons that detect noxious thermal, mechanical, or chemical stimuli (Basbaum et al., 2009). Woolf and colleagues created cell types with different mutations and were then able to grow clones of these cells and characterize the phenotypes associated with each mutation, including key phenotypes such as temperature sensitivity, which replicates what patients experience.

Woolf said they can also interrogate biophysical properties of sodium channels to determine why certain mutations produce particular phenotypes. Beyond disease modeling, they are also able to use these cells for high-throughput, target-based drug discovery, he said. For instance, they have created panels of cells that express different voltage-gated sodium channels, and used these panels to screen for subtype-specific sodium

channel blockers. This is important, he said, because different sodium channels are expressed in different tissues, and it could be dangerous to block a channel that is expressed in cardiac muscle, for example.

According to Woolf, another potentially attractive strategy using the iPSC-CRISPR approach would be to move away from subtype-specific blockers and focus instead on blocking particular cell types or disease states in cells. The advantage of this phenotypic approach is that each cell type has a unique molecular signature in terms of the ion channels expressed. Relatively "dirty" drugs that act on multiple channels with different efficiencies may, in fact, offer advantages for certain disease conditions, he said. Conducting a screen of several thousand compounds annotated to act predominantly on one or several targets could reveal a pattern or signature of compounds that affect a particular phenotype, providing remarkable insight into which pathways are up- or down-regulated in that phenotype, said Woolf. The crucial feature of this approach, he said, is to find a phenotype that is a true surrogate of the human disease state.

Woolf said he thinks it is likely that by using human neurons, it will be possible to develop cell-type and disease-type selective blockers that can provide personalized therapeutics for individual patients, and detect novel agents that act on different cells and different diseases. Stem cells may also be useful to conduct phenotypic screens and screens based on the risk of developing a disease, he said. For example, this approach could allow clinicians to identify in advance patients who are at risk of developing peripheral neuropathy when treated with certain chemotherapeutic agents, and then tailor chemotherapy to the patient. He added that iPSCs could also be used to explore the mechanisms that lead to chemotherapy-induced peripheral neuropathy or to other clinical pain syndromes and identify novel agents that protect against those effects. To accomplish this would require analyzing multiple iPSC lines from deeply phenotyped and genotyped patients, stated Woolf.

### Monitoring and Modulating Circuit Activity in Pain

Robert Gereau, professor of anesthesiology at Washington University, proposed an in vivo approach to assessing neural activity at a cellular-level

resolution using tools developed as part of the BRAIN Initiative,[2] a public–private partnership launched in 2013 to accelerate development of new technologies for mapping brain cells and circuits in order to better understand brain diseases. His lab has been developing optogenetic tools that enable manipulation of neuronal activity in vivo by engineering specific neurons to express light-sensitive proteins, and then using light to entrain action potential firing and manipulate cell function (Copits et al., 2016; Deisseroth, 2011). Gereau said optogenetics provides finer control over the nervous system than was previously possible. By enabling manipulation of subsets of neurons, cell-type specific control is possible, he said.

Early optogenetics studies used implantable fiber optic lasers, said Gereau. More recently he and his colleagues have developed fully implantable, wirelessly powered micro light-emitting diodes (LEDs) (Park et al., 2015), and near-field communication-powered devices implanted in the brain or peripheral structures to provide precise control of neural circuits while at the same time assessing behavioral measures commonly used in animal models. Moving from wired to wireless technologies allows investigators to study responses under more natural conditions, said Gereau. To achieve cellular and subcellular resolution, optogenetics techniques are also used in combination with two-photon microscopy and a virtual-reality behavioral apparatus that allows the animal to be unrestrained, said Gereau.

This technology and others that have been advanced by the BRAIN Initiative are developing rapidly, said Gereau, enabling the identification of cells and circuits that change in association with the development of chronic pain. Steven Hyman, director of the Stanley Center for Psychiatric Research at the Broad Institute, questioned the translatability of this approach to human diseases because they are not working with human cells. Volkow added that integrating all the complex factors relevant for the human condition into these models presents huge barriers. Gereau agreed that many hurdles must be overcome before it will be possible to manipulate circuitry in humans, but to dismiss this as an impossibility ignores the innovation and advances that have been made. He added that neuromodulation and neurostimulation therapies—which are less precise technologies in comparison to optogenetics—are already being used in humans. The promise of being able to get cell-type specificity into these neuromodulatory therapies holds immense promise, he said.

[2]For more information, go to https://www.braininitiative.nih.gov (accessed January 2, 2018).

## Animal Models of Pain

A number of animal models have been developed to recapitulate the elements of pain from stimulus to behavior, and from acute to chronic, said Yaksh. In these animal models, pain may be induced by thermal, chemical, or mechanical injury; may be acute or persistent; and may evoke multiple different physiological (e.g., swelling and erythema) and behavioral (e.g., guarding of the paw, limb movement, vocalization) responses.

These various models have been used successfully in preclinical development of many different classes of drugs to treat different types of pain, said Yaksh. For example, he noted that antagonists, and more recently antibodies against the calcitonin gene-related peptide (CGRP) receptor have been developed for the treatment of migraine based on preclinical studies demonstrating their efficacy (Durham and Vause, 2010; Tso and Goadsby, 2017). However, there have also been a number of drugs that appeared safe and efficacious in preclinical studies, but failed to show clinical efficacy or caused serious side effects in clinical trials, he said. Yaksh noted that while the number of pain drug candidates that move from preclinical to Phase I studies, and then advance to Phase II studies, is only about 11 percent; this figure compares favorably with other disease areas. Some of these compounds are not advanced for strategic or other reasons not reflecting a failure of the preclinical model, said Yaksh. Nonetheless, new approaches are needed to address shortcomings in existing models and to enable longer-term studies, he said. For example, longer-term studies are needed that model chronic inflammatory conditions such as arthritis; that more closely recapitulate the human phenotype; that address spontaneous versus evoked behaviors, thus precluding the need for ongoing handling by investigators; and that enable assessment of reinforcing effects of pain relief, said Yaksh. Volkow added that even when a signal is seen in an animal model, it may not be replicated in a clinical study because humans develop tolerance to the medication. For this reason, she said, preclinical animal models should be evaluated within time windows relevant for the human condition.

Selecting or developing the best model first requires that investigators determine what they are trying to model, such as whether it is evoked or spontaneous, whether it is associated with tissue or nerve injury or inflammation, and whether it is acute or chronic, said Yaksh. To illustrate the challenges, he used the example of fibromyalgia, a condition that affects an estimated two to eight percent of Americans, predominantly women (Clauz, 2014). Fibromyalgia is a clinical diagnosis with no confirmatory

clinical or laboratory endpoint (Fitzcharles et al., 2013), said Yaksh. Diagnosis is based on the presence of multiple non-specific symptoms with no clear etiology. Symptoms include widespread musculoskeletal pain (including temporomandibular joint pain), fatigue, anxiety, affective disorders, dysautonomia, and sleep disorders (Sluka and Clauw, 2016). Of the preclinical models used for fibromyalgia (e.g., intramuscular hypertonic saline, reserpine induced myalgia, and cold stress), none have any particular mechanistic relevance to the pain states as it relates to drug development, said Yaksh.

*Preclinical Efforts Using Companion Animals*

Pathological pain conditions that occur naturally in animals may also provide useful preclinical models. Dorothy Cimino Brown, lead executional scientist for Translational Comparative Medical Research at Elanco, the animal health division of Eli Lilly and Company, runs clinical trials in companion animals, especially dogs. Two types of pain conditions are common in dogs: osteoarthritis and bone cancer. Brown said that of the 72 million owned dogs in the United States, at least 20 percent have clinically significant osteoarthritis, and about 10,000 dogs each year develop bone cancer, usually osteosarcoma. In fact, bone cancer is more common in dogs than in people, she said. The standard of care of canine osteosarcoma is amputation and chemotherapy, but many owners opt for pain management instead of amputation. This choice creates a large population of animals ideally suited for clinical trials of medications in development for bone cancer pain, particularly for novel approaches to pain, said Brown. These trials can support the registration of new treatments for dogs, while at the same time informing human trials, she said. For example, she said that Centrexion Therapeutics is simultaneously developing non-opioid pain therapies for human and canine osteoarthritis that target the TRPV1 (transient receptor potential vanilloid 1) receptor, selectively inactivating local pain fibers that transmit pain signals to the brain.

Supporting the use of companion dogs as models for osteoarthritis treatment studies are the striking parallels between the condition in humans and dogs, said Brown (see Table 3-1). Both experience pain, stiffness, and decreased function due to similar pathogenic mechanisms. Diagnostic and therapeutic approaches are likewise similar. In clinical trials, similar outcome assessments are used, including gait analysis, functional

| OSTEOARTHRITIS (OA) | | | | |
|---|---|---|---|---|
| | | | Humans | Dogs |
| Pathology | Cartilage: | Proteoglycan loss, chondrocyte death, erosion | √ | √ |
| | Subchondral Bone: | Increased turnover, thickening, neovascularization | √ | √ |
| | Joint Margin: | Osteophytes | √ | √ |
| | Synovium & Fat Pad: | Inflammation, fibrosis | √ | √ |
| | Joint Capsule: | Fibrosis, enthesopathy | √ | √ |
| | Muscle: | Atrophy, fat infiltration | √ | √ |
| | | | | |
| Sources of Joint Pain | Direct (contains nociceptors): Subchondral bone remodeling, synovitis, ± joint capsule, ± osteophytes | | √ | √ |
| | Indirect (source of inflammatory catabolites, cytokines, chemokines, neuropeptides): cartilage, ligaments | | √ | √ |
| | | | | |
| Risk Factors | Obesity, age*, trauma* | | √ | √ |
| | | | | |
| Diagnostic Modalities | Radiography, computerized tomography, magnetic resonance imaging, arthroscopy, synovial fluid analysis | | √ | √ |
| | | | | |
| Therapeutic Goals | Control pain and improve function | | √ | √ |
| | Slow progression | | √ | √ |
| | | | | |
| Outcome Assessment in Clinical Trials | Pain, mobility, stiffness, and function indices | | √ | √ |
| | Computerized gait analysis | | √ | √ |
| | Radiography & advanced imaging for disease modification | | √ | √ |

**TABLE 3-1** Similarities Between Humans and Dogs with Osteoarthritis
SOURCE: Presented by Dorothy Brown, October 12, 2017.

To summarize, Yaksh noted that replicating preclinical findings by encouraging detailed reporting of methods and results, incorporating randomization and blinding into preclinical studies, emphasizing effect size and clinical relevance, and routinely including an active control in preclinical modeling could reduce some of the reproducibility issues of preclinical findings and improve the translatability of those findings to the clinical space.

# 4

# Clinical Development of Non-Addictive Pain Medications

**Highlights**

- To move from the preclinical to clinical drug development space, tools such as biomarkers and objective measures of pain and adherence are needed (Koroshetz, Volkow).
- Biomarkers can facilitate drug development by confirming a therapeutic hypothesis, demonstrating target engagement, enabling stratification of potential clinical trial participants, and predicting response to treatment (Ahn, Volkow).
- Subjective measures of pain such as visual analog and numerical pain rating scales are affected by many factors and may be responsible, in part, for high placebo responses and the failure of drugs to show efficacy in clinical trials (Wager).
- Developing new objective measures of how nerves respond to potentially harmful stimuli (i.e., nociception) could provide more accurate, sensitive, and specific endpoints for clinical trials of pain treatments (Volkow).
- Imaging biomarkers such as functional magnetic resonance imaging enables characterization of pain circuitry, insight into pain mechanisms and drug actions, identification of targets, and differentiation of patient subgroups (Wager).
- Imaging-based pain signatures may be useful as enrichment approaches in clinical studies and identify condition clusters (Mackey).
- Pain disorders may be associated with aberrant expression of micro RNAs—measured in the serum as biomarkers—which can provide insight into pain mechanisms and the response to therapy, as well as for patient stratification in clinical trials (Ajit).

- A targeted approach to drug development in well-defined and extensively phenotyped populations may improve the likelihood of showing efficacy, but has risks as well, including not demonstrating an adverse signal until the postmarketing stage and labeling restrictions. This can disincentivize pharmaceutical companies from investing in such products (Diatchenko, Jarow, Hertz, Volkow).
- Deep phenotyping—a comprehensive analysis of phenotypic traits—has shown promise in identifying clusters of patients distinguished by differences in pain sensitivity and psychological distress (Maixner).
- Targeted drug development may be challenging for conditions such as trigeminal neuralgia (a rare chronic condition associated with sudden, severe facial pain), which have no well-defined endpoints (Dawson).
- Incorporating patients into research efforts early in the process of drug development could ensure that outcome measures assess clinically meaningful endpoints and studies are designed in a way that maximizes patient engagement (Veasley).
- The acute-to-chronic pain transition involves multiple mechanisms that drive plasticity-driven changes in the responsiveness of the pain system (Price).
- Preclinical and clinical efforts have begun to improve understanding of the acute-to-chronic pain transition and to identify potential therapeutic targets (Price, Woolf, Yaksh).
- Examining—in a multidimensional way and in collaboration with the Precision Medicine Initiative—the different genetic contributions to pain sensitivity, responsiveness to pain medications, and the transition from acute to chronic pain could provide valuable information in precompetitive space that pharmaceutical companies could build on in developing new treatments (Landis, Volkow).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Despite intense efforts by the pharmaceutical and biotech industries, translating the preclinical identification of new targets into new medicines that will benefit patients and address the opioid crisis has been largely unsuccessful, said John Dunlop, vice president of neuroscience research at Amgen. Preclinical models may fail to predict clinical efficacy for many

reasons. To help companies move from the preclinical to clinical space, Walter Koroshetz said new tools, especially biomarkers to inform Phase II trials, are needed. Objective measures of pain, as well as measures of compliance, such as whether a trial participant is adhering to the study protocol, need to be incorporated into clinical trials, said Nora Volkow, noting that compliance issues, which can be easy to avoid in preclinical studies, may contribute to clinical trial failures.

## BIOMARKERS: A BRIDGE TO CLINICAL STUDIES

In drug discovery for any condition, typically many targets are identified and supported by genetic associations and studies in animal models, said Andrew Ahn. He said the next step requires an important translational leap to enter the framework of clinical opportunity within the pharmaceutical industry. Biomarkers can offer an opportunity to reach across that divide, he said, noting that partnerships are essential in this area given that pharmaceutical companies may not have all the expertise needed to identify mechanisms, connect them to a disorder, and develop tools and assays to move from a mechanistic hypothesis to "druggable" targets and eventually, novel compounds.

Many workshop participants noted that objective markers are needed to demonstrate clinical efficacy of pain medications in development. Currently, the most commonly used pain assessment measures are subjective visual analog and numerical pain rating scales, said Tor Wager, director of the Cognitive and Affective Neuroscience Laboratory at the University of Colorado Boulder

Although these tools are important tools, he said they are influenced by many factors beyond nociception, such as prior beliefs and experiences, emotional reactions, the reporting context, and cultural factors. These factors thus can have a substantial impact on clinical trials and treatment, said Wager. For example, in a trial of a dopaminergic-promoting gene therapy approach for Parkinson's disease, the trial failed because patients receiving the placebo improved to the same degree as those receiving the active drug (Olanow et al., 2015), which may be due in part to the subjective nature of the outcome assessment. Indeed, said Wager, placebo response in clinical trials has been increasing over the years while drug effects have not increased in magnitude, shrinking the drug–placebo difference and making it more difficult to get drugs to market (Tuttle et al., 2015).

## A Case Study of Biomarker-Based Drug Development

As an example of how biomarkers can fuel drug development, Ahn described the development of the monoclonal antibody galcanezumab, which Lilly is currently developing for the treatment of migraine and cluster headache. In 1990, investigators at Prince Henry, Prince of Wales Hospital in New South Wales, New Zealand, demonstrated an increase in blood levels of the vasoactive peptide called calcitonin gene-related peptide (CGRP) in patients with migraine, suggesting that migraine might be caused by an activation of sensory neurons in the head (Goadsby et al., 1990). Later they showed that triptan antimigraine drugs normalized blood levels of CGRP (Edvinsson, 2001), prompting the successful search by a collaboration of academic and pharmaceutical investigators for CGRP antagonists, said Ahn (Ho et al., 2008, 2014; Olesen et al., 2004).

The success of CGRP antagonists in reducing migraine attacks led to the next important step, said Ahn, the search for an antibody that neutralizes CGRP. Setting the optimal dose to test in clinical trials of these monoclonal antibody therapeutics has been facilitated in part by the availability of a biomarker of peripheral target engagement, which involves injecting into the skin a small amount of capsaicin and then measuring to what extent the investigational drug blocks an increase in dermal blood flow (Sinclair et al., 2010). Characterizing pharmacokinetic and pharmacodynamic properties of anti-CGRP antibodies required other assays to measure blood levels of both the antibody and CGRP in relation to migraine symptoms. Ahn showed data from a Phase IIb study of galcanezumab, which demonstrated target engagement and a drug-exposure-biomarker relationship using plasma CGRP level as the biomarker (Kielbasa et al., 2016). Investigators at Lilly recently demonstrated the high sensitivity of two CGRP immunoassays developed by Meso Scale Discovery and Quanterix (Chai et al., 2016).

In short, CGRP biomarkers facilitated the development of this drug by confirming the therapeutic hypothesis, demonstrating target engagement, and tailoring and predicting response, said Ahn.

## Imaging Biomarkers

To qualify as a biomarker, an objective measure of the pain process should reflect the experience of pain, said Wager. He described imaging approaches that are providing new insight about the physiology of the pain response and that may be used to objectively assess pain. For example,

animal studies have demonstrated changes in neuroplasticity in several different brain regions that are linked to the chronic pain response after nerve injury. Human studies are needed to apply these learnings to human brain circuitry, he said. In some cases, this circuitry has already been defined, for example, the CGRP pathway described by Ahn. These biomarkers enable drug developers and clinical trialists to study penetrance, pharmacodynamics, and efficacy, said Wager. The ultimate goal is to identify brain patterns that discriminate drug from placebo, he added. A proof-of-concept study by Duff et al. (2015) shows promise in this regard, said Wager. While these approaches can be used for both drug discovery and repurposing, he noted that a recent consensus statement of the International Association for the Study of Pain concluded that the potential of imaging approaches has not yet been fully realized (Davis et al., 2017).

Wager and others use functional magnetic resonance imaging (fMRI) to characterize pain circuitry and drug actions. He and his colleagues identified an fMRI-based neurological pain signature that captures the neurobiological correlates of evoked pain, starting with heat-induced pain, but then generalizing to other pain conditions (Wager et al., 2013). To validate this approach, they have collaborated with other research groups around the world, testing the construct in different populations and pain types (e.g., electrical, heat, mechanical). These studies suggest that the signature is sensitive and specific to different pain types, as well as being resistant to the placebo effect.

Wager and colleagues have also shown that pain may be mediated by distinct circuits. One of these circuits in the ventromedial prefrontal cortex (vmPFC) plays an important role in learned avoidance—for example, learning to avoid choices that involve pain—and is susceptible to cognitive interventions (Woo et al., 2015). He added that in humans, evidence also suggests that the shift from acute to chronic pain involves corticostriatal circuitry and a shift from classic nociceptive targets to more emotion-focused correlates of pain in the vmPFC (Baliki et al., 2012). This shift could present a problem for treatments focused on the periphery and the spinal cord, he said.

Neuroimaging thus may have implications for treatment selection and development of preventive approaches, said Wager. These objective imaging measures will augment but not replace pain reports, he said, noting that they can provide insight into mechanisms, define targets for intervention, define biotypes or groups of participants that have different neurological and neurophysiologic bases for disorders, and measure physiological component processes. Wager added that biomarkers do not

always have to measure objective pain, but can also measure other outcomes such as cognitive impairment, fear, and avoidance. By linking neuroimaging to other measures of genetics, behavior, heart function, inflammation, and other markers, a clearer understanding of pain may emerge that can help validate new therapies in development, he said.

Another imaging-based pain signature was described by Sean Mackey, chief of the Division of Pain Medicine at Stanford University, working with the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) research network.[1] A recent publication from MAPP compiled clinical data as well as structural and functional MRI data from more than a thousand patients at 7 sites, including patients with urological chronic pelvic pain (localized and widespread) (Kutch et al., 2017). Using machine learning approaches, a signature was identified involving increased connectivity in the frontoparietal cortex, which predicted who would get better and who would worsen, said Mackey. This type of biomarker could be used to identify and exclude patients who are likely to improve even without treatment from clinical studies, he said. Similar approaches have also been used to identify brain-based biomarkers for depression, which he said drives home the point that brain biomarkers and biological markers are needed, along with symptom reporting, to identify condition clusters and tease apart factors that affect response to treatment.

### miRNA Biomarkers

Many pain disorders are associated with aberrant expression of small, non-coding RNAs called micro RNAs (miRNAs), according to Seena Ajit of Drexel University. Approximately 10 years ago, scientists discovered that these regulators of gene expression circulate in the serum, suggesting that they could represent blood-based biomarkers of disease (Chen et al., 2008; Mitchell et al., 2008). Ajit and colleagues have been studying miRNA expression in complex regional pain syndrome (CRPS), a heterogeneous chronic progressive neurological disease characterized by severe pain. Using quantitative polymerase chain reaction analysis, they showed that 18 miRNAs are differentially expressed in CRPS patients, clustering into three groups based on expression levels of these 18 miRNAs (Orlova et al., 2011). Three inflammatory markers were also elevated in patients, and the levels of these markers correlated with pain levels, suggesting that miRNA profiling could be used for patient stratification, according to Ajit.

[1]For more information, go to http://www.mappnetwork.org (accessed January 2, 2018).

Her lab has also explored miRNA expression in several different rodent models of neuropathic and inflammatory pain, where they identified characteristic expression profiles and two miRNAs that were common with CRPS patients (Qureshi et al., 2016). Identification of these miRNA biomarkers enabled Ajit and colleagues to do mechanistic studies that elucidated disease processes and demonstrated that miRNA profiles were altered by therapeutic intervention, said Ajit. Similarly, in patients with CRPS, good and poor responders to ketamine treatment can be differentiated by change in their miRNA profiles, suggesting the feasibility of using miRNA signatures as prognostic biomarkers (Douglas et al., 2015).

Ajit and colleagues were also able to show that one of the most downregulated miRNAs in patients compared to controls, miR-939, targets proinflammatory genes. Reduced levels of miR-939 result in an increase in expression of these genes, amplifying the pro-inflammatory pain signal transduction cascade (McDonald et al., 2016).

Ajit's lab has also shown that miRNAs are packaged into exosomes (secreted extracellular vesicles present in bodily fluids), which can cross the blood–brain barrier and facilitate transport and intercellular communication (McDonald et al., 2014). The field is young, she said, so many questions about exosome biology have yet to be answered. She noted that the stability of exosomes in serum makes retrospective studies possible and suggested using serum and plasma samples from failed clinical trials, where the therapeutic outcome is known, to search for miRNA signatures that could be used for patient stratification. For biomarker discovery, she advocated obtaining miRNA profiles beginning in Phase I studies, which may enable later stage trials to be conducted in defined patient subgroups. She added that a centralized database of miRNA profiles and clinical phenotypes could accelerate drug development, but would require adherence to standardized acquisition, analytical, and data normalization protocols.

## A TARGETED APPROACH TO THERAPY DEVELOPMENT IN THE CLINICAL SPACE

A targeted approach to therapy development where drugs are developed and tested in strongly phenotyped, well-defined populations could represent a potentially useful foundational strategy on which to build a public–private partnership, suggested Koroshetz. Sharon Hertz, director of the Division of Anesthesia, Analgesia, and Addiction Products at the Food

and Drug Administration's (FDA's) Center for Drug Evaluation and Research, agreed that defining a subpopulation that is more likely to respond to a drug, and then demonstrating efficacy in that subpopulation, may be a good drug development strategy. However, if a compound in development does not target a specific aspect of a specific disease, and the drug is anticipated ultimately to be used in a more general way, there are dangers to that approach, said Hertz.

For example, anti-nerve growth factors (anti-NGFs) have been developed as analgesics (Chang et al., 2016). Preclinical and clinical testing of the anti-NGF antibody tanezumab suggested efficacy in improving pain and function in patients with osteoarthritis (Miller et al., 2017). However, clinical studies revealed a serious and unexpected adverse effect not found in the preclinical studies: patients treated with the drug had a higher incidence of joint destruction requiring replacement, including in shoulder joints that rarely need replacement, said Hertz. It was determined that there was a destructive arthropathy associated with the active treatment arms, stalling development of the drug while the factors contributing to this risk were determined. Even with this information, calculating a risk/benefit ratio will be challenging, said Hertz, because patients vary considerably in their tolerance for risk and desire for treatment benefits. For example, she noted that patients with debilitating trigeminal neuralgia may be willing to use a drug product with greater risk than patients with milder forms of pain. She also commented that had the anti-nerve growth factor antibody studies started with trigeminal neuralgia, where the population is much smaller, the adverse signal might not have even been detected until the postmarketing stage.

Katherine Dawson, vice president for Late Stage Clinical Development in Pain, Neuromuscular, and Rare Diseases at Biogen, said her company chose to pursue treatments for trigeminal neuralgia precisely because there is an urgent need for therapies due to the severity of the disorder (i.e., increased risk of death due to suicide). She acknowledged that for serious conditions like this, treatments may be introduced even before the safety profile has been fully elaborated. Dawson elaborated that no safety profile is fully elucidated by the clinical trials, as uncommon and rare events will be missed; however, the risk-benefit profile that supports therapeutic development should not be the same as for a treatment focused on an illness or disorder that is not as serious or severe. With this approach, the full population of persons with the disorder will have an opportunity to take the therapy, rather than just those who meeting the inclusion and exclusion criteria, she said. Dawson noted that Biogen faced a similar dilemma when

three patients being treated with natalizumab in clinical trials developed progressive multifocal leukoencephalopathy and two died. The drug was temporarily taken off the market, but was reintroduced with restrictions. Developing treatments for trigeminal neuralgia is particularly challenging, she said, because there are no well-defined endpoints, patients experience both spontaneous and evoked pain, and the severity fluctuates. She added that in order to pursue interventions in this population, Biogen has worked closely with patient groups and the FDA to identify what endpoints are meaningful to patients.

Moving forward with drugs that target novel pathways thus requires careful and thoughtful consideration, said Hertz. Ken Verburg, senior vice president at Pfizer and asset team leader for tanezumab, agreed that developing a drug in a small population can be risky. In the pharmaceutical industry, a failed early study means a failed drug program, he said, even though the drug may be beneficial in certain situations. To avoid this problem, he advocated testing a drug in three different models where the failed trial scenario is low. For example, is a drug intended for pain useful for molar extraction, osteoarthritis, and postherpetic neuralgia? If a network of physicians skilled in doing clinical investigational work were available, this pathway might be traversed fairly quickly, he said. In addition, Verburg cited the need for more exploratory work developing new clinical trial study paradigms.

William Maixner described another program that has used deep phenotyping of thousands of individuals, along with machine learning and clustering methodologies to identify common and unique pathways in chronic pain conditions. Using a comprehensive array of biopsychosocial measures, the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study identified three clusters of individuals distinguished by pain sensitivity and psychological distress (Bair et al., 2016). These clusters could be reproduced by taking into account only four variables—semantic awareness, anxiety, depression, and pain sensitivity—which Maixner suggested could be incorporated into a short questionnaire given in the clinic. His team is now conducting pragmatic trials after classifying individuals with this set of variables. They are also working with Luda Diatchenko to identify molecular signatures associated with each group, which could suggest subgroup-specific targets, leading to the creation of new chemical entities or the repurposing of existing compounds to target these clusters.

## PREVENTING THE ACUTE-TO-CHRONIC PAIN TRANSITION

High on the priority list of the federal pain research strategy is preventing the acute-to-chronic pain transition, said Koroshetz. He noted that the National Institutes of Health Common Fund team has taken on this topic as a potential project. Theodore (Ted) Price, director of Systems Neuroscience at University of Texas, Dallas, described the transition from acute to chronic pain as a plasticity-driven event that persistently alters the responsiveness of the pain system. Important mechanisms involved in this transition include neuroimmune and peripheral immune interactions and neuronal plasticity. Phenotypic changes in subsets of neuronal, immune, and other types of cells may drive this transition, he said. Important questions he raised that emerge from this model include whether targeting these mechanisms will reverse the transition, returning someone to a pain-free or normal acute pain state, and whether treatments currently being used impact the transition or conversion to chronic pain.

### Preclinical Perspective

Price suggested that preclinical models can provide insight into the acute-to-chronic pain transition and possibly illuminate ways to stop, reverse, or prevent it from occurring. One of these models, the hyperalgesic priming model, posits that an acute inflammatory insult, such as injection of prostaglandin $E_2$ ($PGE_2$), triggers transient hyperalgesia as well as long-lasting hypersensitivity (Reichling and Levine, 2009). This reaction can be blocked with a single dose of a μ-opioid agonist; however, repeated exposure to a μ-opioid agonist induces opioid tolerance. (Joseph et al., 2010). Price noted that simply exposing an animal multiple times to the opioid can also cause conversion to the chronic pain state (Araldi et al., 2015). His lab has also shown that hyperalgesic priming can be blocked by ablating neurons in the dorsal horn that express neurokinin 1 (NK-1),[2] suggesting that these neurons are required for hyperalgesia priming (Kim et al., 2015). However, Price said that if animals are primed prior to blocking NK-1 neurons, there is no effect on priming, arguing against the use of NK-1 antagonists as a treatment for intractable pain.

[2]NK-1 receptors have been studied in the brain and spinal cord to understand affective behavior, nociception, and emesis.

Another preclinical model, the "latent sensitization" model, also suggests that the transition to chronic pain involves priming that causes long-lasting sensitization of pain pathways, and results in a predisposition to chronic pain (Taylor and Corder, 2014). These models offer the potential of identifying neural circuits that contribute to chronic pain, said Price. For example, work in his lab suggests that dysfunction of the dopaminergic system may play a critical role in pain chronicity (Megat et al., 2017). He added that stress primes animals for the acute-to-chronic pain transition, and is being actively investigated in conjunction with these other models. Moreover, Price stated that priming models are useful to predict efficacy of various analgesics for the treatment of chronic pain, as well as to predict whether an acute pain treatment can prevent priming and the transition to chronic pain.

He added that a better understanding of the mechanisms underlying the acute-to-chronic pain transition may suggest therapeutic approaches to reverse the transition and treat chronic pain. Price cited three hypothesized chronic pain resolution mechanisms that are currently under investigation in preclinical models: the resolvins, immune modulators, and adenosine monophosphate-activate protein kinase (AMPK) hypotheses. The resolvin hypothesis suggests that the resolvins, a unique family of lipid mediators, may reduce inflammatory pain both centrally and peripherally (Xu et al., 2010). The immune modulator hypothesis suggests that CD8+ T cells and increased interleukin-10 may promote recovery from persistent neuropathy following cancer treatment (Krukowski et al., 2016). Price mentioned two potential interventions related to this mechanism that might prevent the development of or even reverse chronic pain: an IL4-10 fusion protein delivered intrathecally (Eijkelkamp et al., 2016) and exercise-induced release of IL-10 (Grace et al., 2016). Price's lab is pursuing a third hypothesis, the AMPK activation hypothesis, which suggests that AMPK activators may also prevent development of or reverse chronic pain (Asiedu et al., 2016).

Preclinical models also have revealed sex differences in the acute-to-chronic pain transition, said Price. For example, CGRP antagonists have profound effects in female rodents, but do nothing in males. Given that migraine is predominantly a female disease, CGRP antagonists may be extraordinarily effective, he said.

Clifford Woolf of Harvard Medical School suggested it may be possible to use induced pluripotent stem cell (iPSC) lines from well-phenotyped and -genotyped patients to explore the acute-to-chronic pain conversion.

While some people use the term "transition," he said the word "conversion" more accurately reflects that change from one set of neurobiological processes that cause acute pain to another set of processes that cause chronic pain. Comparing iPSC lines derived from patients who developed chronic pain from ones who did not could help identify the underlying pathways or targets involved, he said. Moreover, once candidate drugs have been identified, iPSCs from many different patients could be used for multiple in vitro trials, with no concerns about placebo effects.

Tony Yaksh said there are also inflammatory models that produce more persistent and long-lasting pain responses (Christensen et al., 2016), and may reflect the conversion from acute to chronic pain.

### Clinical Efforts to Prevent the Acute-to-Chronic Pain Transition

There are also many efforts to develop new pain treatments, but there has been less attention devoted to developing interventions that could prevent the acute-to-chronic pain transition, said Robert Dworkin, professor of anesthesiology and perioperative medicine, neurology, and psychiatry at the University of Rochester. Such studies could test various models of prevention, including the following conditions in which the acute-to-chronic pain transition often occurs:

- Surgery, leading to chronic postsurgical pain;
- Acute low back injury leading to chronic low back pain;
- Wrist fracture, leading to CRPS;
- Cancer chemotherapy, leading to peripheral neuropathy;
- Herpes zoster and the development of postherpetic neuralgia; and
- Diabetic peripheral neuropathy.

The burden of chronic pain associated with these conditions is high, said Dworkin. For example, postsurgical pain persists in between 10 and 50 percent of cases, varying with the type of surgery (Kehlet et al., 2006), although Dworkin said it is unclear whether severe acute pain itself is a causal risk factor or concomitant to nerve or musculoskeletal damage. Mackey added that surgery is nothing more than a controlled injury and thus, the perioperative period provides a unique environment in which to study what happens before and after injury.

Dworkin suggested two broad types of studies that need to be done, preferably in tandem: (1) observational studies to develop a better understanding of risk and protective factors, transition mechanisms, and biomarkers of transition; and (2) clinical trials to test putative preventive interventions. Some of the risk factors are well established, he said. For example, the severity of acute pain and the severity of nerve or musculoskeletal injury increase the likelihood that chronic pain will develop and persist. A prior history of chronic pain and psychosocial vulnerabilities such as catastrophizing—i.e., the irrational belief that something is worse than it actually is—also raise the risk of developing chronic pain, he said. Dworkin added that some people may also be at increased risk because of underlying mechanisms that could facilitate the transition from acute to chronic pain, such as impaired conditioned pain modulation or augmented central sensitization.

Fifteen years ago, Dworkin and Dennis Turk, from the University of Washington, launched the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT),[3] which has since convened 20 meetings to build consensus on how pain trials should be conducted. Dworkin said he thinks trials of putative preventive interventions can and should be started right away using recommendations published in 2015 (Gewandter et al., 2015). For example, patients scheduled for cancer chemotherapy or surgery could receive preventive interventions a week or two before the cancer treatment or surgery. He added that multiple follow-ups should be done. Possible primary endpoints could include incidence of and time to resolution of any chronic pain or clinically important chronic pain, pain intensity after 6 months, and various area under the curve analyses, said Dworkin. In addition, he advocated for including hypothesized transition biomarkers in all studies.

Examples of prevention trials that Dworkin said could be soon include those that would deliver anti-NGF antibodies perioperatively in patients scheduled for knee replacement or thoracotomy, and brief targeted catastrophizing interventions such as cognitive behavior therapy in patients with acute low back injury. He also mentioned that while three clinical trials of vitamin C for prevention of CRPS have produced conflicting results, this low-risk intervention should be tested further. Ultimately, he said that preventing the acute-to-chronic pain transition will likely require multimodal intervention, including pharmacological and non-pharmacologic treatments, such as physical therapy and psychological treatment.

[3]For more information, go to http://www.immpact.org (accessed December 27, 2017).

Mackey proposed that clinical studies also explore the continuum of pain and trajectories of pain using duration as a dependent variable to determine what factors cause pain to be persistent, what leads patients to persistently use opioids, and what characteristics lead to resilience. He noted that surgery is a risk factor for persistent opioid misuse and abuse. Thus, it provides an opportunity to better understand what factors contribute to persistent opioid use and design interventions to mitigate this problem. Volkow added that patients who are treated with opioids for chronic pain tend to have higher levels of pain, suggesting that opioids themselves may facilitate the conversion to chronic pain, possibly through common mechanisms of neuroplasticity and conditioning. Past and current history of smoking increases the risk for developing chronic pain conditions like temporomandibular disorders, said Maixner. Price said the preclinical data also support this idea—giving a μ-opioid agonist at the time of injury seems to promote neuronal plasticity, while inverse agonists[4] precipitate a more transient pain state (e.g., Kandasamy and Price, 2015).

Volkow noted two other factors known to increase the risk of converting to chronic pain: being female and catastrophizing. Catastrophizing invokes multiple circuits, she said, and she wondered if differences have been identified between XY and XX cells. Catastrophizing is a heritable trait, said Diatchenko, but to study this at the genetic level first would require identification of all the elements that comprise catastrophizing. Woolf added that while this could be studied in vitro, it would require many fully genotyped cell lines from a diverse set of individuals to get a sense of line-to-line variation. Robert Gereau agreed that catastrophizing is an important predictor of poor pain outcome for patients undergoing surgery. He suggested that mapping genetic susceptibility in terms of cognitive flexibility could have a substantial impact on understanding catastrophizing, and that it could have translational implications in terms of intervening to prevent long-term pain.

## REGULATORY CHALLENGES RELATED TO THE APPROVAL OF PAIN MEDICATIONS

According to Diatchenko, some pharmaceutical companies fear that technologies identifying subgroups of patients who will respond to particular treatment will reduce the generalizability of a drug and be reflected in

[4]Agents that bind to the same receptor as agonists, but induce an opposite response.

the labeling of the product. Hertz commented that restricted labeling would be preferable to failure. Jonathan Jarow, senior medical advisor at the FDA, noted that using predictive biomarkers in a clinical trial can lead to labeling that requires a companion diagnostic, which can create some problems. Moreover, he noted that predictive biomarkers can be very complex. For example, expression of programmed death-ligand 1 (PD-L1) can predict the response of some tumors to some drugs (Patel and Kurzrock, 2015) and thus, the labeling of these drugs may indicate that they should be used only for certain types of tumors that overexpress PD-L1, said Jarow. But for other tumor types, many responders do not express the biomarker, and therefore, the biomarker is not required in the labeling for those indications, he added.

Prognostic biomarkers used for trial enrichment can include more general phenotypic characteristics such as weight or physical signs and usually do not require a companion test, said Jarow. However, there is still a possibility that this could affect labeling. He added that a surrogate endpoint is "very problematic," and will require validation that it is reasonably likely to predict clinical benefit. The FDA generally restricts the use of surrogate endpoints to serious conditions where the event rate (e.g., death) is very low or it takes a long time to see the event, he said. For example, in the early development of HIV drugs, viral titer at 12 weeks was accepted as a useful endpoint to get the drug to market more rapidly, said Jarow.

# 5

# Therapeutic Development for Opioid Use Disorders and Overdose Prevention and Reversal

**Highlights**

- Identifying new targets for opioid use disorders, including targets not based on the μ-opioid receptor or that address addiction neurocircuitry, could lead to the development of new treatments, including those that suppress withdrawal symptoms (Volkow, Walsh).
- Developing a biomarker for vulnerability to addiction could increase understanding of why some people but not others become addicted, and identify new therapeutic targets that are less likely to trigger addiction (Volkow).
- Developing new molecular entities, including opioid-sparing medications for pain and ancillary medications that may reduce dose escalation and the development of tolerance, would not only provide new therapeutic opportunities, but could also elucidate mechanisms that have limited the effectiveness of existing medications (Walsh).
- Challenges in designing trials for opioid use disorder treatments include the difficulty of establishing reasonable inclusion and exclusion criteria, the decision whether to use a placebo control or active comparator, and the selection of meaningful outcome measures (Walsh).
- The Food and Drug Administration (FDA) has demonstrated flexibility in setting the requirements for approval of drugs to treat opioid use disorders and there are now three treatments currently available—methadone, naltrexone, and buprenorphine (Walsh).
- Improving access to existing FDA-approved medications to reverse overdose could be accomplished by removing barriers such

as the need for prior authorization, which may be imposed for drugs classified as controlled agents because of their potential for abuse (Walsh).

- Given the complex mechanisms that contribute to addiction, combining existing medications to treat opioid use disorders may be needed (Volkow).
- Exploring new uses for existing medications that could be repurposed for the treatment of opioid use disorders could hasten the entry of new therapies to market (Volkow, Walsh).
- Extended release formulations of buprenorphine are in development that offer long-term opioid receptor blockade (Heibreder).
- Vaccines that produce high levels of specific antibodies against oxycodone and hydrocodone would neutralize and prevent these drugs from reaching the brain, and thus may reduce opioid abuse and prevent addiction in high-risk individuals (Volkow, Walsh).
- Through a public–private partnership between the National Institute on Drug Abuse and private-sector partners, a nasal spray formulation of naloxone called Narcan®, which is used to reverse overdose, was developed and received FDA approval quickly (Crystal).
- Integrating treatment of opioid use disorders into the health care system and incorporating new technologies might enable more comprehensive and effective treatment (Nickel).
- Developing practice guidelines on treating flare-ups in patients with chronic pain who have developed an opioid addiction could help primary care and other providers deliver more effective care (Walsh).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Roger Crystal, chief executive officer of Opiant Pharmaceuticals, Inc., noted that the United States is somewhat unique in that opioids are the first line of analgesia in hospital-based and dental settings. Furthermore, he said that systems in the United States incentivize the broader use of opioids, adding that even if opioid prescriptions were halted, there would still be millions of opioid addicts who need better treatment. Moreover, while overdose levels from opioid painkillers appear to be tapering off, they are being replaced by even greater overdoses from synthetic opioids such as fentanyl, said Crystal. Fentanyl is not only much more potent than heroin,

it gets into the brain quickly and lasts longer, and is cheaper and easier to produce, he said. It is also easy to derivatize.

Opioid use disorder is a chronic relapsing brain disease that is expressed as compulsive behavior and that is accompanied by robust physical dependence, said Sharon Walsh. The diagnostic criteria for a substance use disorder, according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) (American Psychiatric Association, 2013), includes 11 behavioral characteristics with the level of severity based on the number of behaviors present (see Figure 5-1). Walsh noted that physical dependence is not required to meet the criteria for opioid use disorder, although distinguishing those who do or do not have physical dependence would be important for drug development studies.

Three treatments are currently available for treating opioid use disorder by targeting opioid receptors, said Walsh. Methadone was introduced in the 1970s, followed by oral naltrexone in 1984, sublingual buprenorphine (Suboxone®) in 2002, injectable naltrexone (Vivitrol®) in 2010, and most recently, buprenorphine implants (Probuphine®) in 2016. Methadone is a full agonist, buprenorphine a partial agonist, and naltrexone an antagonist of the opioid receptor, said Walsh. She noted that buprenorphine is on the World Health Organization's list of essential medicines—highlighting the importance of treating this disorder, according to Walsh—and development of the buprenorphine implant was facilitated by a partnership between Titan and Braeburn Pharmaceuticals, with some support from the National Institute on Drug Abuse (NIDA).

None of these drugs are a panacea, said Walsh, because more than half of patients relapse within 6 to 11 months. But this is far better than the 100 percent relapse in the first month among people who try to stop the drug without treatment, said Walsh. Treatment with these drugs decreases opioid use, overdose deaths, criminal activity, and infectious disease transmission, while increasing social functioning, she said.

According to Walsh, the clinical studies that were required to gain approval of drugs to treat opioid use disorders indicate that the FDA is willing to think creatively about their expectations for different types of medication. For example, only one pivotal study was required to file a New Drug Application for Probuphine; and for two other long-acting injectable formulations of buprenorphine, sponsors used the 505(b)(2) pathway, which required them only to do bridging studies, a blockade study, and a Phase III efficacy and safety study. Both of these drugs were also granted priority review by the FDA.

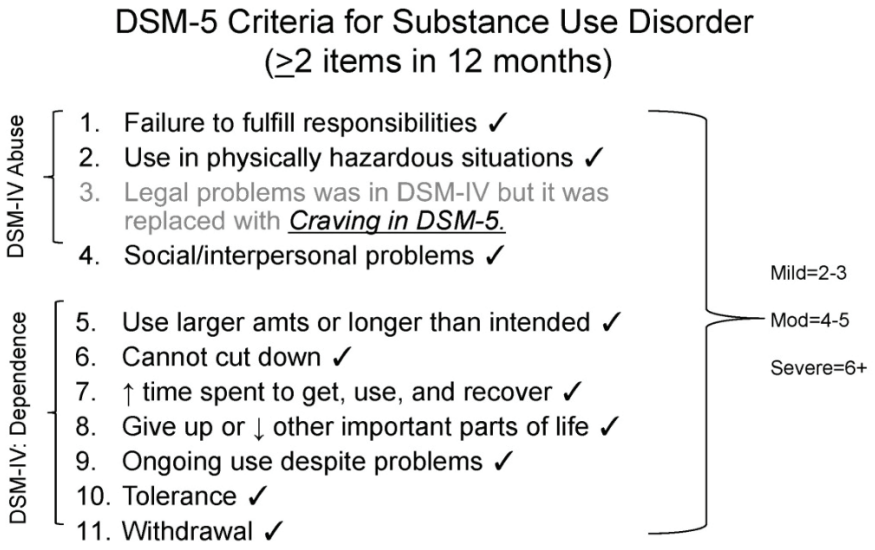


**FIGURE 5-1** DSM-5 criteria for substance use disorder. Whereas the DSM-4 separated abuse and dependence into two disorders, the DSM-5 moved to a single defining disorder that varies in severity based on the number of behavioral characteristics present.
SOURCES: Presented by Sharon Walsh, October 11, 2017; APA, 2013.

Buprenorphine, a high-affinity μ-opioid receptor partial agonist, received FDA approval as a sublingual tablet, either alone or in combination with naloxone, for the treatment of opioid addiction in 2002.[1] It works through several different mechanisms to suppress opioid withdrawal symptoms, reduce craving and produce opioid blockade, said Walsh. Opioid blockade is a phenomenon whereby a drug blocks the response to an opioid such as hydromorphone. While several preclinical models exist, Walsh illustrated opioid blockade with data from a recent study she conducted with colleagues at the University of Kentucky's Center on Drug and Alcohol Research. In this randomized clinical trial of CAM2038, a subcutaneous buprenorphine depot formulation, individuals were enrolled who were physically dependent on opioids and not seeking treatment for their disorder. In five 3-day sessions, participants were given one of three doses of hydromorphone and were asked to rate how much they liked it on

[1]For more information, go to https://www.fda.gov/Drugs/DrugSafety/ucm191521.htm (accessed December 27, 2017).

a visual analog scale. Following the first test session, participants were randomized to receive different doses of CAM2038, along with the hydromorphone. As expected, there was a dose-related increase in liking for hydromorphone, but when they were dosed with the CAM2038, there was a complete and automatic suppression of this response (Walsh et al., 2017).

This outcome indicates that the drug may be able to prevent relapse, Walsh said. Nora Volkow of NIDA noted that buprenorphine and naltrexone also have the effect of improving mood, possibly by blockade of kappa receptors, which could contribute to their therapeutic effect. However, Walsh said that what patients want is a drug that will treat the symptoms of withdrawal—they want to feel well, have their cravings go away, and they want to stop thinking about using drugs every day. For this to happen, other types of drugs are needed, she said.

## NEW TREATMENTS IN DEVELOPMENT FOR OPIOID USE DISORDERS

Novel approaches to treating opioid use disorders are in development, said Walsh. One such drug is lofexidine, an α-adrenergic agonist, which is being developed for the treatment of withdrawal symptoms by a small company called World Meds, with substantial support from NIDA. In a recent Phase III trial of this medication conducted by Walsh and colleagues, lofexidine was shown to significantly suppress the symptoms of opioid withdrawal (compared with placebo) in patients who had opioid use disorder, were physically dependent, and were willing to undergo spontaneous withdrawal (Gorodetzky et al., 2017).

Walsh stressed, however, that detoxification alone is not an efficacious treatment for opioid use disorder and, in fact, is highly predictive of overdose and death. She cited a study from Sweden that compared patients who received a short 7-day taper off buprenorphine (the detoxification arm) to those who received buprenorphine for 1 year (Kakko et al., 2003). Both groups also received counseling and psychosocial services. After 60 days, no one in the detoxification arm remained in the study, and 4 of the 20 people randomized to that arm died. Similarly, people are entering very expensive 90-day residential treatment programs that prohibit medication, and one week after getting out they are overdosing and dying, said Walsh.

Nonetheless, she said there is an important application for drugs such as lofexidine because they can provide a bridge to manage symptoms for people transitioning from opioids or agonist therapies to antagonists like

naltrexone. They are also useful for people seeking a medication-free status so they can meet work requirements or enter a residential program, and for chronic pain patients who want to transition from opioid to non-opioid treatments or discontinue agonist treatment.

Long-acting formulations of buprenorphine are also in development. According to Christian Heidbreder, chief scientific officer of Indivior, Inc., these drugs are needed because with daily dosing of a drug such as buprenorphine, the plasma level of drug at the end of the dosing interval is subtherapeutic (Greenwald et al., 2007). If patients are not covered for the entire dosing interval, he said, there can be reemergence of opioid-like effects, craving, and withdrawals. In addition, there is a potential for diversion and misuse with oral medications such as these, he said.

Heidbreder described the clinical development of an alternative buprenorphine formulation (RBP-6000), which uses an extended release drug delivery platform that combines buprenorphine with a biodegradable polymer and a biocompatible solvent and is delivered once a month by subcutaneous (SC) injection with a prefilled syringe. A Phase II clinical study conducted by Heidbreder and colleagues showed that 12 weeks of treatment with RBP-6000 (300 mg) completely blocked the subjective drug liking effects of a full opioid agonist such as hydromorphone (Nasser et al., 2016). Modeling and simulation based on positron emission tomography (PET) data suggested that 300 mg of RBP-6000 in subjects with opioid use disorder would translate into plasma concentrations of buprenorphine $\geq$ 2 ng/mL and 75 to 92 percent occupancy of the μ-opioid receptors in the brain.

This led to a Phase III 24-week multicenter trial in treatment-seeking patients who met the DSM-5 criteria for moderate or severe opioid use disorder, followed by an open-label safety extension study. Patients were first inducted with SUBOXONE® (buprenorphine/naloxone) sublingual film over a period of 7–14 days and then randomized to one of following dosing regimens: 6 once-monthly 300 mg doses, 2 once-monthly 300 mg doses followed by 4 once-monthly 100 mg doses, or 6 once-monthly SC injections of placebo. In addition to study medication, all subjects received manual-guided psychosocial support at least once a week. The Phase III study showed that the mean percentage abstinence was significantly higher in both RBP-6000 groups (approximately 40 percent) compared with placebo (5 percent). Exposure-response analyses confirmed a relationship between buprenorphine plasma concentrations, predicted brain μ-opioid receptor occupancy, abstinence, opioid craving, and withdrawal

signs/symptoms. In conclusion, treatment with RBP-6000 significantly reduced illicit opioid use compared to placebo with an acceptable safety/tolerability profile in adults with opioid use disorder, said Heidbreder.

Basic research is also needed to identify new targets for opioid use disorders that are not based on the μ-opioid receptor but that modulate endogenous opioids or that address neurocircuitry disruption by addiction, said Volkow. Other strategies, including the development of vaccines that target heroin, oxycodone, and fentanyl are also in development, said Walsh, noting that nearly all this work is supported by NIDA rather than industry. For example, researchers at the University of Minnesota have developed a vaccine to induce serum antibodies that bind to oxycodone and hydrocodone, preventing these drugs from getting into the brain, she said. In rodents, the vaccine has been shown to reduce the amount of oxycodone self-administration, suggesting that the vaccine may reduce opioid abuse (Pravetoni et al., 2014).

## Special Considerations for Conducting Trials for Opioid Use Disorder Treatments

Enrolling participants in trials for opioid use disorder treatments can be challenging because of the unique characteristics of the intended population, said Walsh. Among the inclusion and exclusion criteria that will need to be carefully considered are poly-substance abuse, liver function, venous access, and co-morbid mental health disorders and infectious diseases such as hepatitis C and HIV, which are common in this population, she said. Other important considerations include the possibility of deception when using self-report measures; preparing for adverse events, including unplanned pregnancies, overdose, and seroconversion (time period in which HIV antibodies become detectable); and planning for adherence issues related to transportation, arrests, and other reasons for impairment. Walsh added that enrolling patients in grave danger of death because of their untreated opioid use disorder into studies of extended release formulations (e.g., young people who endure long hospitalizations for conditions such as endocarditis or osteomyelitis), might improve the efficiency of studies while potentially reducing relapses and saving lives.

In addition, some trial design considerations include whether to use a placebo or active comparator as a control. Given that there are some partially effective treatments available, Walsh said she favors active comparator controls, although these require use of non-inferiority designs. Selecting the appropriate outcome measures can also be challenging, and

the FDA is thinking creatively about the expectations for different types of drugs, said Walsh. For example, urine drug toxicology levels may be appropriate for assessing whether abstinence is achieved or if a relapse has occurred, although there are no fixed criteria to determine this. Moreover, Walsh suggested that more attention should be paid to other measures such as improvement of quality of life and psychosocial factors such as maintaining employment and mending relationships with family members. She also noted that substance use disorder patients are recognized as a protected population under the Code of Federal Regulations (CFR Title 42: Part 2), which requires drug developers to take into account state laws regarding reporting and other issues related to confidentiality.

## THERAPEUTIC DEVELOPMENT TO REVERSE OVERDOSE

Naloxone has been around for a long time to address the immediate emergency issue of treating opioid overdose, said Roger Crystal. It was originally approved as an injectable that required trained personnel to administer. An autoinjector was recently made available, but remains expensive and still involved needles; therefore, less suitable for lay bystanders. The concept of the nasal spray began when some first responder and harm reduction groups began using improvised nasal kits. These were not FDA approved, the absorption of naloxone was poor (Dowling et al., 2008), and they required an eight-step process to prepare them for use. What was needed, said Crystal, was a product that could be easily delivered by a lay-bystander with sufficient efficacy to deliver naloxone into the brain quickly to prevent hypoxia.

Recognizing the urgent need to develop a product that could be easily and quickly delivered to people by anyone in the midst of an overdose, Opiant partnered with NIDA to develop a nasal spray formulation that would deliver a high dose of naloxone in a small volume quickly and easily. Opiant had previously developed a nasal spray formulation of naloxone to treat binge eating disorder, said Crystal. The data from the pilot study conducted in collaboration with NIDA showed that both 2 mg and 4 mg intranasal doses were rapidly absorbed and produced higher blood levels compared to the standard 0.4 mg intramuscular dose (Krieter et al., 2016). The product, NARCAN® nasal spray, was licensed to Adapt Pharma in December 2014 and received FDA approval in November 2015, and was on the market by the first quarter, 2016. Crystal noted that the

device can be used in all directions and does not need priming, easing delivery even in a crisis situation.

# 6

# Public–Private Partnerships to Advance Pain and Opioid Use Disorders Research and Development

**Highlights**

- Public–private partnerships (PPPs) have been proposed and are under development by National Institutes of Health in two domains—one focusing on opioid use disorders and the other on developing more effective non-opioid pain medications, or non-addictive opioid medications (Volkow).
- Building partnerships that engage stakeholders across the entire process of treatment development, from the point of discovery all the way through insurance reimbursement, including pharmaceutical and device industries, and patients across the entire age and socioeconomic spectrum would ensure that all perspectives are incorporated and addressed (Koroshetz, Ostrovsky, Shurtleff, Veasley, Volkow).
- PPPs benefit patients and families by increasing access to currently available treatments and promoting the possibility of new medicines and technologies, and better care (Nickel, Powers).
- Given the complexity and broad impact of chronic pain and the opioid epidemic across many fields, multidisciplinary partnerships that foster collaborations outside neuroscience might open new possibilities for therapeutic development (Heidbreder, Kaufmann, Powers).
- Because data on compounds and clinical studies that emerge from PPPs inform payer decisions, it will be important for investigators to consider how data will be interpreted and used by payers early in the development process (Ling, Ostrovsky).

- Quality measurements in clinical studies are key, but to inform payer decisions, the evidence must go beyond supporting clinical and analytic validity and include clinical utility (Ling).
- PPPs are necessary to bridge the translational gap between preclinical and clinical studies and to advance the goals of the National Pain Strategy (Ahn, Mackey).
- A PPP for a preclinical testing platform could catalyze the discovery and characterization of non-addictive molecules for the treatment of pain, enable better prediction of the efficacy of new treatments, and ensure robustness and reproducibility of data (Kehne).
- Other suggested partnerships include a precompetitive consortium about target identification and validation, and a partnership to repurpose shelved compounds for pain (Flores, Maixner, Potter).
- Creating a clinical trials network for chronic pain would allow coordinated and more efficient testing of novel treatments in more heterogeneous populations, including lower income and minority populations and children, which is essential for developing treatments that are effective in the real world (Koroshetz, Ostrovsky, Veasley, Volkow).
- The Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) PPP is a collaboration with the Food and Drug Administration to accelerate the discovery and development of new analgesic, anesthetic, addiction, and peripheral neuropathy medicines (Dworkin, Hertz).
- Developing alternative formulations of treatments for opioid use disorders, including abuse-deterrent and longer lasting formulations, could make treatment more accessible, especially to people in rural communities with no nearby physicians specialized in this area or clinics (Heidbreder, Volkow).
- Potential goals of PPPs for opioid use disorders include understanding the pharmacogenetics of addiction medicine, developing biomarkers for vulnerability of addiction, patient stratification, and improving clinical trial endpoints, as well as patient-outcome endpoints (Heidbreder, Volkow).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

The meetings convened by NIH in 2017 to gather input about how to respond to the opioid epidemic (see Chapter 1) concluded that public–private partnerships (PPPs) were needed in two different domains, said Nora Volkow. One domain would address the need to develop more effective non-opioid pain medications or non-addictive opioid medications, and the other is to better develop treatments for opioid use disorders and for reversing overdose, she said. She envisioned that the pain partnerships would be a more classic PPP with investment by academia, government, and industry in precompetitive space through the development of resources to accelerate drug development, while the opioid use disorder partnership would be targeted more toward interactions in competitive space by engaging industry in the development of medications. There is strong support at the highest levels of government to prioritize the treatment of addiction and pain, she said, noting that the Food and Drug Administration (FDA) will play a key role and is highly motivated to help to try and facilitate easier regulatory pathways for novel products.

## PUBLIC–PRIVATE PARTNERSHIPS TO ACCELERATE DEVELOPMENT OF NON-ADDICTIVE PAIN MEDICATIONS

Volkow said that in discussions with pharmaceutical and biotech companies working in the pain therapeutics space, a major roadblock emerged regarding the sharing of data that pertains to efforts on successful and failed drug developments for pain. A PPP could address this problem by establishing a shared database, although Volkow acknowledged that legal issues will need to be addressed in order for this to become a reality. Other points endorsed at the stakeholder meetings convened by the National Institutes of Health (NIH) included the creation of a research trial network, the development of biomarkers to demonstrate target engagement and stratify patients for trials, the development of objective measures of pain sensitivity, reengineering preclinical platforms to have better predictive efficacy, and applying new technologies to improve pain drug discovery, said Volkow. Robert Gereau pointed to the example of the BRAIN Initiative, which was launched in 2003 and has already produced an abundance of new technologies that enable the identification of cells and circuits that change in association with the development of chronic pain. The BRAIN Initiative has achieved this not only through the infusion of funds, but also

by bringing diverse groups of investigators together to work on big problems, which Gereau said is the type of change needed in the pain field.

Some partnerships have already been established to advance the strategic goals of the National Pain Strategy, said Sean Mackey. For example, his group is involved in the multicenter consortium for pelvic pain called the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP). Through 11 sites, the MAPP consortium enabled collection and analysis of imaging data that led to the discovery of an imaging-based pain signature for pelvic pain discussed in Chapter 4. Mackey also has collected large amounts of data through the Collaborative Health Outcomes Information Registry (CHOIR), which was established in response to the Institute of Medicine's report *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research* (IOM, 2011). CHOIR uses an open-source learning health care platform to develop a deep signature of individual patients across multiple dimensions of physical, psychosocial, and social functioning. Mackey said it has been "incredibly informative" as to what drives pain and leads to persistence of pain. For example, social isolation and social satisfaction appear to be key drivers for patients with pain, as well as those with addiction, he said.

These partnerships are important, said Mackey, because they enable the collection of large aggregated amounts of data, which need to be integrated into clinical trials in order to understand the characteristics of heterogeneous populations. However, he noted that for every patient brought into a clinical study, nine are typically excluded, often leading to homogeneous populations of "simpler" patients who may not represent the broader population.

William Maixner suggested that the primary goal of a pain consortium might be to collect and integrate data from large human cohort studies, develop subpopulations, and do molecular profiling to begin validating targets and developing new chemical entities or repurposing existing compounds. A second goal, he said, would be to develop new bioinformatics tools for target discovery. Third, Maixner cited the need to conduct mechanistic studies and cellular studies for both reverse and forward translation.

Walter Koroshetz said that a problem companies have made in the past was trying to solve big problems with a single drug, only to shut down the whole program when the drug failed to reach its primary endpoint. While "multiple shots on goal" are clearly needed, he advocated what he called "developing a beachhead" by focusing first on the target most likely to yield success, such as calcitonin gene-related peptide (CGRP) in migraine,

before generalizing to a vast array of pain conditions, i.e., moving step by step rather than trying to address everything at the same time.

### Partnership for a Preclinical Testing Platform to Catalyze Discovery of Novel Drugs

John Kehne of the National Institute of Neurological Disorders and Stroke (NINDS) proposed a PPP to develop a preclinical testing platform that would catalyze the discovery and characterization of non-addictive modalities—small molecules, biologics, and devices—for the treatment of pain. Such a partnership would enable the design of a rigorous, centralized, and flexible screening engine to generate robust data, provide a means of evaluating agnostically early-stage targets and leads, and promote translation of discoveries into new drugs, said Kehne. Chris Flores of Johnson & Johnson suggested that this platform also promote standardization and the use of informatics approaches, and consider many themes mentioned throughout the workshop, including the importance of spontaneous versus evoked pain behaviors. He also advocated focusing on validated targets, including cannabinoids, the opioid receptor, and various ion channels. John Dunlop of Amgen added that the platform should be accessible to academics and both small and large companies, so that all are getting the same high-quality data. Incorporation of genome-wide association studies (GWASs), more systematic use of human cell-based models, and development of large panels of cell lines could also lead to the identification of new targets and improve translation, he said. Dunlop also supported extending the preclinical testing platform to include companion animals.

As partners in this collaboration, NIH would provide developers free-of-charge access to resources for testing and characterizing promising leads, including medicinal chemistry and drug metabolism and pharmacokinetics, said Kehne. He noted that the similar NINDS-funded Anticonvulsant Screening Program (ASP), currently known as the Epilepsy Therapy Screening Program or ETSP, has already proven successful. Since ASP's creation in 1975, the program contributed substantially to advancing nine new epilepsy therapeutics to the market, said Kehne. He maintained that a similar preclinical testing program for non-addictive pain medications would incentivize researchers to pursue discovery and development of novel therapies by providing valuable tools, resources, and expertise while reducing the cost burden associated with drug development. Tony Yaksh noted that this could be especially valuable for smaller pharmaceutical companies that may not have, or may have cut

back, preclinical pain modeling resources. Existing NIH infrastructure for sample handling, testing, and data management would be made available to the research community, and the proposed partnership would add value beyond the ETSP model by accessing collective capabilities, scale, and resources from other partners, said Kehne. Equally important, the program would generate high-quality data for various models to support new business partnerships and applications for additional funding, he said. Finally, he suggested that harnessing the collective expertise and resources of partnering organizations would enable development of testing funnels, protocols, and reporting structures.

To create this partnership, Kehne said it will be important to find the right balance of robust assays, configure these assays into streamlined flowcharts with identified milestones, and build capacity for model development and refinement. A flexible decision-making process, qualified staff, and a commitment from partners to share all data generated by the partnership are other critical elements, said Kehne. He proposed a 5-year plan to launch the partnership, test targets and compounds, develop models, and evaluate progress. Maixner added that the partnership should include a prioritization process whereby an efficacy risk assessment is conducted for all the medications of interest to determine what will be advanced relative to what is available now.

Robert Dworkin, director of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION),[1] noted that preclinical studies may fail to predict efficacy in Phase II studies for reasons other than a failure of the model. For example, the Phase II study may have been underpowered. In such cases, a company may simply drop the program without exploring the reasons for the Phase II failure, he said. An additional goal of the preclinical testing platform could be to explore why the preclinical model was not predictive of the Phase II results and apply the learnings from those studies to improve future preclinical testing programs, said Koroshetz.

### Accelerating Translation with a Network for Clinical Pain Research

One important goal of a PPP would be to develop a clinical network for pain that goes beyond enabling more efficient clinical trials, but also enables discovery research, said Volkow. Key components of discovery

[1]For more information, go to http://www.acttion.org (accessed December 27, 2017).

research that were addressed at the workshop include identification of biomarkers, including biomarkers that predict toxicity, said Volkow. Koroshetz suggested that a clinical research network could accelerate the process of moving from discovery to therapy by providing the tools industry needs to make investments with higher predictability that they will pay off, for example, biomarkers and assays for target validation.

Putting together a clinical research network to do biomarker studies, deep phenotyping, and clinical trials will require streamlined operations and platforms that improve quality and efficiency, said Petra Kaufmann, director of Office of Rare Diseases Research at the National Center for Advancing Treatment Sciences. A single Institutional Review Board review, streamlined contracting, and improved data management systems, for example, can shorten the time to launch and complete a clinical study, she said. Shared or master protocols implemented with both traditional and novel paradigms for defining populations, such as those discussed in Chapter 4, and novel trial designs such as adaptive designs should also maximize the efficiency of studies and promote a deeper understanding of mechanisms, she said. Observational studies and biomarker validation studies that are conducted in parallel with clinical trials would also maximize the impact of these studies, said Kaufmann. Finally, she suggested integrating electronic medical records available at academic and health care centers into clinical data research warehouses to promote learning and help generate hypotheses.

Dworkin said the value of an analgesic clinical trials network is unequivocal, pointing to the success of similar networks established in other disease areas, such as the Huntington's and Parkinson's study group, oncology cooperative groups, and NeuroNEXT,[2] a clinical trials innovation network established by NINDS. To develop an analgesic clinical trial network, about 30 clinical trial sites could be selected, with both a junior and senior investigator at each site, and including pediatric sites. These investigators would be brought together for a training program led by biostatisticians and clinical trialists, prior to road-testing a clinical trial in the network by testing an analgesic medication with established efficacy versus placebo, said Dworkin.

One of the difficulties in establishing a clinical trial network for chronic pain is the fact that pain conditions are frequently managed by either primary care physicians or specialists from different areas (e.g., gy-

[2]For more information, go to http://www.neuronext.org (accessed December 27, 2017).

necology, oncology, rheumatology, and urology) rather than by pain specialists in neurology or anesthesiology, said Christin Veasley. Kaufmann agreed that the network would have to be multidisciplinary and suggested that this may be possible by actively involving patients who could drive this. Scott Powers added that demonstrating success in one area can attract other specialties to a network, similar to what was seen in building the cystic fibrosis network. Identifying champions for the network concept in various disciplines may also breed success, said Powers. Koroshetz commented that recognition of an opioid crisis might also incentivize the establishment of new structures such as a network for pain research that would lead to improved pain care and reduced reliance on opioids.

Jonathon Jarow said the FDA is supportive of platform trials, master protocols, and networks. Real-world data can be helpful in identifying clinical trial sites that have been successful in enrolling patients for various types of studies. Jarow suggested that because industry may be reluctant to submit their assets to platform studies, a network for pain research might consider a demonstration project with vitamin C or some other off-the-shelf compound. He added that the 21st Century Cures Act[3] created a space called innovative trials and will begin funding pilot projects in early 2018, with statistical support.

Koroshetz suggested that another strategy might be to challenge existing heavily resourced programs with diverse expertise such as NIH's Clinical and Translational Science Awards (CTSA) to respond to the opioid crisis. Story Landis also mentioned the "hub and spoke" strategy that NINDS used for its stroke network. For pain, the hubs could be specialty clinics, with spokes going out to primary care. As with stroke, this could help build bridges between acute and rehabilitative care for patients with pain, she said.

Several workshop participants mentioned the importance of data sharing, noting that capitalizing on the increasing willingness of companies to share data, compounds, and expertise may enhance opportunities to build precompetitive partnerships. Volkow added that data sharing efforts on both successful and failed drug development efforts would help researchers learn from both their successes and failures.

Volkow said the workshop made clear the value of a clinical network for pain. Now the key challenge is to translate this recognition into a program that is sustainable and that has the resources and expertise to back it

[3]For more information, go to https://www.congress.gov/bill/114th-congress/house-bill/34 (accessed on January 2, 2018).

up, she said. A second key challenge is to ensure that outcomes reflect what is most important to patients and at the same time are quantifiable, reproducible, and standardized to enable creation of large datasets that will provide information on long-term outcomes.

### *Pediatric Considerations for a Clinical Trial Network*

The inclusion of pediatric sites in a clinical trial network is essential, said Powers, because clinicians are taking care of patients every day with imprecise knowledge about pain management. Children are not little adults, but they are willing and able to participate in clinical trials, said Powers. Moreover, pediatric specialists across disciplines have demonstrated the ability to collaborate and execute clinical trials, for example, through the Cystic Fibrosis Therapeutic Development Network.[4] Powers cited an additional advantage of networks beyond the efficiencies mentioned by Kaufman. Networks create friendships that help investigators navigate the ups and downs of clinical studies as a team. They promote a sense of purpose and common goals.

Powers also recognized the vulnerability of children and adolescents, and suggested that some of the regulatory policies concerning safety and protection may need to be reconsidered for studies involving pediatric populations. However, he also suggested that waiting until adult studies are completed before enrolling children has slowed the development of effective treatments for children. Children and families interested in participating in studies have to wait far too long, and that needs to change, he said. Sharon Hertz said there is no regulatory barrier for starting pediatric clinical trials concurrently with adult studies; however, industry may be reluctant to take on pediatric studies because of perceived risks of studying a drug in children that is not known to have a clear safety profile.

## PARTNERSHIPS TO ADDRESS OPIOID USE DISORDERS AND REVERSE OVERDOSE

Collaboration is needed in many areas of drug development because the expertise in industry is not matched in academia, said Sharon Walsh. However, she said that in the area of opioid use disorders, most expertise

[4] For more information, go to https://www.cff.org/Research/Researcher-Resources/Therapeutics-Development-Network (accessed January 2, 2018).

resides in academia, where many researchers are eager to work with companies to develop new therapeutics. Academic labs, for example, have the expertise to conduct basic research on abuse liability, she said.

Walsh noted that there are many joint funding opportunities through National Institute on Drug Abuse (NIDA) that are specifically designed to bring people together across academia and industry. Another organization that promotes collaboration in this area is the College on Problems of Drug Dependence, the longest standing scientific organization in the United States. that has been dedicated to strengthening science on drug use disorders to improve therapeutic development, said Walsh.

One of the lowest hanging fruits for safer opioids are abuse-deterrent formulations, said Volkow, yet these approaches are utilized in less than 3 percent of all prescriptions, presumably because they are much more expensive. She added that if payers are not incentivized to cover these medications, pharmaceutical companies may be reluctant to invest in developing them. This is an area where patient advocates have played and can continue to play a critical role in trying to change the conversation about reimbursement and parity across Medicaid, Medicare, and private insurers, she said.

Alternate formulations and development of novel approaches to addressing opioid addiction are in development as described in Chapter 5, but the urgency of the problem demands more attention and more resources, noted several workshop participants. Volkow noted that repurposing existing medications and combining these medications to improve outcomes may also prove beneficial, but have not been prioritized by industry. Christian Heidbreder suggested that PPPs might also focus attention on studying the effectiveness of extended-release buprenorphine and/or other treatments in patient subpopulation programs; exploring the pharmacogenetics of addiction; and developing programs to deliver extended release formulations of buprenorphine in emergency department settings as a way of preventing opioid overdose and subsequent relapse to drug-seeking and drug-taking behaviors.

There has also been interest in developing biomarkers for vulnerability of addiction, which could increase understanding of why some people but not others become addicted, and identify new therapeutic targets that are less likely to trigger addiction, said Volkow, adding that NIDA has been working for many years in this area. Heidbreder added that biomarkers are also needed for patient stratification and endpoints in clinical trials. New patient-outcome measures that address the impact of treatment on quality

of life also need to be developed and validated, along with tools to understand the mechanisms of and assess craving, he said. Heidbreder also argued that a public–private partnership should scrutinize research using preclinical addiction models with a focus on reliability and reproducibility of published data. Finally, to make meaningful changes in the opioid use disorder landscape, he suggested a need for an interdisciplinary approach that involves the engagement of several disciplines, including engineering, chemistry, physics, and mathematics.

William Potter, senior advisor at the National Institute of Mental Health (NIMH), wondered if multiple partnerships are needed to address different paths individuals take on the road to addiction, such as physical or psychological pain. Indeed, Volkow noted that only a small minority of patients who are prescribed opioid analgesics for pain management ever develop an opioid use disorder (estimated around 10 percent) and about 20 percent of individuals with opioid use disorder started out with pain. The overprescription of opioid medications for pain, however, led to their diversion and facilitated the illicit use of opioid medications for their rewarding effects, she stated. Andrey Ostrovsky, then chief medical officer for the Center for Medicaid and CHIP (Children's Health Insurance Program) Services, added that components of the heroin epidemic differ markedly from city to city. For example, in one city the predominant heroin product may be black tar from Mexico, while in another city it might be carfentanil sent through the mail from China. Joblessness, despair, stigma, and other psychological and sociologic components that contribute to addiction also vary across cities, said Ostrovsky. David Shurtleff added that self-medication for disorders such as depression, anxiety, posttraumatic stress disorder, and trauma also contribute to the huge increase in the incidence of opioid use disorders. The complicated nature of the problem argues strongly for a public–private partnership, with one pillar focusing on developing medications and strategies to treat opioid use disorder, and another on new medications for pain, said Shurtleff.

Other crosscutting partnerships proposed at the workshop included a precompetitive consortium on target identification and validation, which was advocated by Flores. Potter also endorsed this idea, noting that when multiple companies are pursuing the same target, it would be useful to better understand what differentiates their compounds by using the same assays. Also proposed by Flores and Maixner was a PPP between pharmaceutical and biotech industries and academia, to put forward shelved compounds that could be tested in preclinical pain and addiction models for potential efficacy and repurposing.

## UNDERSTANDING THE ROLE OF PAYERS IN SUPPORTING THERAPEUTIC DEVELOPMENT FOR PAIN AND OPIOID USE DISORDERS

Shari Ling, deputy chief medical officer for the Centers for Medicare & Medicaid Services (CMS), described how the output of clinical studies, including potential studies emerging from the PPPs previously described, informs coverage decisions made by CMS. Quality measurements are key, she said, and evidence must go beyond supporting clinical and analytic validity, which is required for FDA approval, to clinical utility. Ling said she was heartened to hear workshop participants focusing on co-morbidities and what matters most to patients and families. CMS requires patients to be at the center of studies, with determination of risks and benefits central to coverage decisions for treatments as well as diagnostic and prognostic tests, she said.

Because of the complexity of the Medicare population, co-morbidities are a particular challenge in the context of how Medicare views data and evidence, said Ling, noting that arthritis, cancer, and several other conditions associated with high pain levels are common in this population. One of the major reasons that evidence may fall short in Medicare determinations is that it was collected in non-Medicare populations with the expectation that findings would be generalized to the Medicare populations, she said.

Ling advised that it is never too soon for investigators to begin thinking about how data will be interpreted clinically and translated into information useful to beneficiaries. Phenotypes that are well described in a clinical setting and biomarkers of clinical pathways need to inform the utility and value of treatments and diagnostic tests, she added. As health care moves away from fee-for-service to alternative payment models in which there may be shared management across primary and specialty care, the focus must remain on outcomes that are meaningful for patients and families, said Ling. The CMS Innovation Center[5] has the authority to test new care and payment models, and recently issued a request for information regarding possible demonstration projects in that area, including projects to lower the cost of prescription drugs and provide mental and behavioral health services for beneficiaries, including those affected by the opioid crisis.

[5]For more information, go to https://innovation.cms.gov/About (accessed January 2, 2018).

Ostrovsky focused his remarks on how to get new innovations paid for through Medicaid, which is the largest insurer in the United States, covering about 75 million individuals per year at an annual cost of about $500 billion. Because Medicaid is a federal–state partnership, both the federal government and states participate in coverage decisions. For example, states submit plans for how they want to pay for pharmacologic and non-pharmacologic approaches to treating opioid use disorders, chronic pain, and acute pain. Most state plans are accepted by CMS. However, with state budgets constrained by declining tax revenues, even new therapeutics with strong supporting data may face state restrictions on coverage, said Ostrovsky. States are also exploring alternative payment programs such as bundled payments and Medicaid Health Homes, rather than fee-for-service for substance use disorders. Ostrovsky suggested that new public–private partnerships consider approaching states early to learn about their concerns regarding coverage of novel therapeutics and diagnostics.

## FINAL REMARKS

Koroshetz reflected on the workshop presentations, noting that the stories shared by Veasley and Jessica Hulsey Nickel set the stage for framing discussions around what is important for patients. The pain treatment and opioid crises have now surpassed the AIDS crisis in terms of the number of people who die each year, he said, yet the resources dedicated to finding effective, non-addictive treatments for pain and addiction are low in comparison to what has been allocated for AIDS. While the field is expanding rapidly, he noted that the time frames for moving a compound from discovery to an approved drug are unacceptably long and must be accelerated enormously. To accomplish this, he suggested emphasizing the development of tools that industry needs to make their investments with high predictability that they are going to pay off, including platforms such as clinical research networks that enable testing of multiple drugs in parallel rather than sequentially.

Shurtleff added that a long-term strategy is needed that incorporates new technologies and tools to move drugs through the development pipeline more quickly. Moreover, because many factors contribute to the pain syndrome, therapies will need to incorporate both medications and behavioral approaches, he said. Patients must be at the center of the treatment plan, Shurtleff continued, which involves both letting them take control of their own treatment and being part of the therapy-development process.

# A

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# B

# Workshop Agenda

**Advancing Therapeutic Development for Pain and Opioid Use Disorders Through Public–Private Partnerships: A Workshop**

October 11–12, 2017
Keck Center | Room 100
500 Fifth Street, NW | Washington, DC

**Background:** Pain is a leading cause of disability in the United States, affecting more people than cancer, diabetes, and heart disease combined. Many physicians have come to prescribe opioids to their pain patients, and pain patients have come to expect such prescriptions. The resulting dramatic increase in opioid prescriptions within the past decade has been a major factor contributing to the opioid epidemic that the country currently faces, with alarming rates of misuse, abuse, and overdose deaths. The dramatic increase in the cost of Naloxone—the only Food and Drug Administration–approved opioid overdose reversal medication—has made it more challenging to gain access to the live-saving medication. In the 2011 Institute of Medicine report *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, the committee advocated a multidisciplinary approach for pain research and public–private partnerships (PPPs) to improve the process for developing new pain medications. While several initiatives are underway to enhance pain research and improve care in the country, including the National Institutes of Health (NIH) Pain Consortium and Interagency Pain Research Coordinating Committee's *National Pain Strategy*, additional efforts are needed to foster collaborations between the public and private sectors in

order to reduce the adverse risks of prescribed opioids and to accelerate the development of non-opioid medications.

In June and July 2017 NIH hosted three small meetings focused on creating PPPs to address the urgent public health need associated with opioids. NIH is joining with private partners in the pharmaceutical industry and the research community to launch an opioid research initiative with the goal of cutting in half the amount of time required to develop new therapies for (1) safe, more effective strategies for pain management; (2) new and innovative opioid addiction treatments; and (3) overdose reversal interventions. The Forum on Neuroscience and Nervous System Disorders proposes to host a public workshop bringing together key stakeholders to (1) advance the discussions that emerged from the three NIH meetings held in June and July 2017 to address the opioid epidemic, and (2) examine potential implementation barriers and opportunities related to the proposed approaches discussed.

**Workshop Objectives:**

- Review the state of the science for opioid and non-addictive pain treatments.
  - Provide an overview of emerging pain models, including those in the peripheral nervous system (e.g., induced pluripotent stem cells and human experimental biology).
  - Discuss the progress on the identification and validation of targets and biomarkers (neuroinflammation, genetic, proteomics, etc.). Explore whether there is a systematic methodology to validating biomarkers to determine their usefulness.
  - Examine approaches to testing new formulations and drugs, and discuss the patient populations needed for those clinical trials.
  - Consider the formulation of promising pain medications—beyond opioid analgesics—that may have been shelved by companies.
- Explore opportunities and challenges to changing the formulation of marketed prescription opioids to decrease misuse, addiction, and potential overdoses (e.g., different delivery systems and antitampering mechanisms).
- Consider regulatory issues related to the approval of pain medications and discuss potential opportunities to address those challenges.

- Discuss public–private partnerships that might facilitate and de-risk the development of drugs to treat opioid overdoses and non-addictive therapeutics for pain (e.g., an Accelerating Medicines Partnership for pain). Highlight lessons learned from industry and opportunities to advance the development of these drugs (e.g., a designated clinical trial network for pain).

## Day One: October 11, 2017

1:30 p.m. Welcome and Overview of the Workshop
STORY LANDIS, Vice Chair, Forum on Neuroscience and Nervous System Disorders, National Academies of Sciences, Engineering, and Medicine (*Co-Chair*)
WALTER KOROSHETZ, National Institute of Neurological Disorders and Stroke (*Co-Chair*)

1:45 p.m. The Opioid Epidemic and State-of-the-Science on Therapeutic Development for Pain
NORA VOLKOW, National Institute on Drug Abuse (*Co-Chair*)

2:05 p.m. Living with Pain: A Patient's Perspective
CHRISTIN VEASLEY, Chronic Pain Research Alliance

2:20 p.m. The Federal Pain Research Strategy: An Overview
LINDA PORTER, National Institute of Neurological Disorders and Stroke

2:40 p.m. Discussion Among Speakers and Workshop Participants

3:10 p.m. BREAK

### SESSION I: THERAPEUTIC DEVELOPMENT FOR OPIOID USE DISORDERS

Objectives: Discuss potential methods for developing extended release formulations of marketed medicines for opioid use disorders and

overdose prevention and reversal. Consider lessons learned for drug development for opioid use disorders and explore the utility of shelved compounds as potential therapeutics.

3:25 p.m. Session Overview
NORA VOLKOW, National Institute on Drug Abuse (*Moderator*)

3:35 p.m. Patient Advocate
JESSICA HULSEY NICKEL, Addiction Policy Forum

**Case Studies**

3:45 p.m. Extended Release Formulations for Opioid Use Disorders
CHRISTIAN HEIDBREDER, Indivior Inc.

4:05 p.m. Overdose Reversal
ROGER CRYSTAL, Opiant Pharmaceuticals, Inc.

**Drug Development**

4:25 p.m. Facilitating Therapeutic Development for Opioid Use Disorders: An Academic Perspective
SHARON WALSH, University of Kentucky

4:45 p.m. Discussion Among Speakers and Workshop Participants

5:45 p.m. Day One Wrap-Up
*Workshop Co-Chairs*

6:00 p.m. Adjourn Day One

## Day Two: October 12, 2017

8:30 a.m. Day Two Opening Remarks
*Workshop Co-Chairs*

### SESSION II: IDENTIFYING OPPORTUNITIES FOR THERAPEUTIC DEVELOPMENT IN NON-ADDICTIVE PAIN MEDICINES

Objectives: Innovative public–private partnerships are needed for the development of safe, effective, and non-addictive pain treatments. Incentives will be necessary to encourage pharmaceutical and biotechnology company investment in this space. What new targets exist and what would be required to accelerate the process of moving toward therapeutics for non-addictive pain medicines?

8:35 a.m. Session Overview
JOHN DUNLOP, Amgen (*Moderator*)

**Novel Methods for Identifying Targets for Pain**

8:45 a.m. Genomic/Genetic Approaches
LUDA DIATCHENKO, McGill University

9:00 a.m. Identifying Potential Targets for Pain Management Using Human Cells/Organoids, Tissue
CLIFFORD WOOLF, Harvard Medical School

9:15 a.m. Monitoring and Modulating Circuit Activity in Pain–Promise of the BRAIN Initiative
ROBERT GEREAU, Washington University in St. Louis

9:30 a.m. Discussion Among Speakers and Workshop Participants

**What Can Be Done to Improve Target Validation in Developing Non-Addictive Pain Medicines?**

10:00 a.m. What Has Worked and What Hasn't Worked in the Preclinical Space to Predict Success
TONY YAKSH, University of California, San Diego

10:15 a.m. What New Preclinical Efforts Are Needed to Improve the Process of Therapy Development (e.g., Companion Animals)?
DOROTHY CIMINO BROWN, Elanco Animal Health

10:30 a.m. Can a Public–Private Partnership Engineer Preclinical Testing Platforms with Better Predictive Validity?
JOHN KEHNE, National Institute of Neurological Disorders and Stroke

10:45 a.m. Discussion Among Speakers and Workshop Participants: *Launching Public–Private Partnerships to Accelerate the Development of Therapeutics for Non-Addictive Pain Medicines*

11:15 a.m. BREAK

**SESSION III: ADDRESSING CLINICAL CHALLENGES AND IMMEDIATE NEEDS**

Objectives: Discuss challenges and opportunities to identifying and validating objective biomarkers of pain, including approaches focusing on homogenous populations. Consider mechanisms that might block the acute to chronic pain transition. Explore the role of a public–private partnership to advance therapeutic development for pain (e.g., a designated clinical trial network for pain).

11:30 a.m. Session Overview
WALTER KOROSHETZ, National Institute of Neurological Disorders and Stroke (*Moderator*)

**Developing Biomarkers to Aid Phase II Studies of Target Engagement and/or Proof of Principle**

11:40 a.m. An Industry Perspective on Biomarker-Based Drug Discovery
ANDREW AHN, Eli Lilly and Company

11:55 a.m. Imaging
TOR WAGER (*via WebEx*), University of Colorado Boulder

12:10 p.m. miRNA Biomarkers
SEENA AJIT, Drexel University

12:25 p.m. Discussion Among Speakers and Workshop Participants

12:40 p.m. PANEL: How to implement a targeted approach to therapy development by focusing on homogenous populations; dissecting pain mechanisms and clinical research in specific pain conditions—natural history biomarkers, clinical trial readiness.

KATHERINE DAWSON, Biogen
SHARON HERTZ, Food and Drug Administration
SEAN MACKEY, Stanford University
WILLIAM MAIXNER, Duke University
KEN VERBURG (*via WebEx*), Pfizer Inc.

1:20 p.m. LUNCH

**Process to Developing Therapies to Prevent the Acute to Chronic Pain Transition—What Is Needed?**

2:00 p.m. Preclinical Perspective
THEODORE PRICE, The University of Texas at Dallas

2:15 p.m. Clinical Perspective
ROBERT DWORKIN, University of Rochester Medical Center

2:30 p.m. Discussion Among Speakers and Workshop Participants

2:45 p.m. PANEL: A U.S. Network for Pain Research (Including Pediatric Research). Where's the Value?

ROBERT DWORKIN, University of Rochester Medical Center
PETRA KAUFMANN, National Center for Advancing Translational Sciences
SCOTT POWERS, Cincinnati Children's Hospital

3:15 p.m. Discussion Among Speakers and Workshop Participants: *Launching Public–Private Partnerships to Advance Clinical Work in Understanding and Treating the Transition from Acute to Chronic Pain*

3:45 p.m. BREAK

## SESSION IV: MOVING FORWARD AND NEXT STEPS

Objectives: Synthesize and discuss key highlights from the workshop presentations and discussions and, most importantly, identify next steps and promising areas for future action and research.

4:00 p.m. Workshop Synopsis and Potential Next Steps
*Moderator*: STORY LANDIS, Vice Chair, Forum on Neuroscience and Nervous System Disorders, National Academies of Sciences, Engineering, and Medicine (*Co-Chair*)

Session I: NORA VOLKOW, National Institute on Drug Abuse
Session II: JOHN DUNLOP, Amgen
Session III: WALTER KOROSHETZ, National Institute of Neurological Disorders and Stroke
Discussants: DAVID SHURTLEFF, National Center for Complimentary and Integrative Health

SHARI LING, Centers for Medicare & Medicaid Services
ANDREY OSTROVSKY, Center for Medicaid and CHIP Services

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|---|---|
| 4:25 p.m. | Discussion Among Moderators and Workshop Participants |
| 4:55 p.m. | Final Comments |
| 5:00 p.m. | Adjourn |

# C

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