The 9th Annual NIH Pain Consortium Symposium on Advances in Pain Research:
Biological and Psychological Factors that Contribute to Chronic Pain

WORKSHOP SUMMARY

Natcher Conference Center
National Institutes of Health
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# ABBREVIATIONS AND ACRONYMS

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<th>Acronym</th>
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<tr>
<td>CBT</td>
<td>cognitive behavioral therapy</td>
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<td>cLBP</td>
<td>chronic low back pain</td>
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<td>CNS</td>
<td>central nervous system</td>
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<td>CSF</td>
<td>cerebrospinal fluid</td>
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<td>IC</td>
<td>interstitial cystitis</td>
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<td>ICs</td>
<td>Institutes and Centers</td>
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<td>IL</td>
<td>interleukin</td>
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<td>IOM</td>
<td>Institute of Medicine</td>
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<td>IPRP</td>
<td>Interagency Pain Research Portfolio</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<td>OA</td>
<td>osteoarthritis</td>
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<td>SNI</td>
<td>spared nerve injury</td>
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<td>TMD</td>
<td>temporomandibular joint dysfunction</td>
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<td>TRP</td>
<td>transient receptor potential</td>
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EXECUTIVE SUMMARY

On May 28–29, 2014, the National Institutes of Health (NIH) Pain Consortium convened The 9th Annual NIH Pain Consortium Symposium on Advances in Pain Research, with a specific emphasis on biological and psychological factors that contribute to chronic pain.

This annual symposium highlights advances in pain research sponsored by NIH supported investigators. More than 20 NIH Institutes and Centers (ICs) and offices participate in the Pain Consortium [1] and in this yearly symposium.[2]

This gathering of an expert group of scientists, patient advocates, and clinicians to discuss the current state of research on biological and psychological factors underlying chronic pain was timely for providing important guidance on future directions for the field.

This symposium’s theme is aligned with the recommendations contained in the 2011 Institute of Medicine (IOM) report Relieving Pain in America, which called for a comprehensive strategy for pain prevention, treatment, management, and research on a population level.[3] Achieving this goal requires a multidisciplinary and collaborative approach to identifying and pursuing key areas for future research.

THE BIOLOGY AND PSYCHOLOGY OF CHRONIC PAIN

Chronic pain prevalence is increasing, with more than 100 million Americans affected.[3] Forty-two percent of adults report daily pain. Chronic pain costs the United States approximately $635 billion per year,[4] with higher prevalence and annual costs than cancer, HIV/AIDS, heart disease, diabetes, and Alzheimer’s disease.

The nature and experience of chronic pain are complex, vary widely among individuals, and depend on a combination of biological, psychological, and social factors. The neurobiology of pain involves communication across numerous regions in the brain and spinal cord. Factors that modulate these connections include the extent of a disease or injury, prior history of pain, trauma, or stress, and genetic or other predisposing elements. Pain itself can cause physiological changes that further heighten a person’s risk for transitioning to chronic pain. Psychological factors, including emotional and cognitive context, also significantly affect the experience of pain and an individual’s level of functioning in the face of pain.[3]

Researchers are just beginning to understand these complexities. Teasing apart the underlying factors of both acute and chronic pain—at the molecular, cellular, systems, and environmental levels—is essential for developing more effective
treatments and care for individuals with chronic pain, as well as for preventing the transition from acute to chronic pain in those who are vulnerable.

RESEARCH HIGHLIGHTS

Pain and Depression

Presenters in the first session explored the bidirectional relationship between pain and depression and possible treatment avenues. Experts in the field are beginning to recognize that comorbid depression may be part of the larger syndrome of centralized pain, characterized by pain, fatigue, sleep disturbances, memory problems, and psychiatric symptoms. There is a need to move the focus to investigating the pathophysiology of centralized pain, instead of simply pain and depression. Another historical focus of pain research has been negative emotions and factors that predispose people to chronic pain (i.e., vulnerability factors). Recent studies indicate however, that positive emotions and other factors that protect people from developing chronic pain (i.e., resilience factors) are often diminished in chronic pain.[5] Resilient responses to pain or stress, such as positive social contact and increased positive affect, may counteract the effect of vulnerability factors. In animals, social interaction similarly reduces nerve injury–associated neuroinflammation, allodynia, and depressive-like behavior. Mindfulness meditation, a promising approach for treating chronic pain and depression is associated with multiple pain-relieving mechanisms, including coping strategies (e.g., acceptance),[6] positive mood,[7] cognitive reappraisal,[8] and emotional and cognitive control.[9]

Pain and Sleep Disorders

Presenters in the second session focused on the genetic basis for risk of chronic pain and pain-related sleep disorders which are frequently comorbid, the effects of cognitive behavioral therapy (CBT) on comorbid insomnia and pain, and potential inflammatory markers associated with effects of sleep disruption on pain and mood. Risk for chronic pain and sleep disorders appear to share genetic underpinnings, as illustrated in the case of genetic, familial sleep disorders that feature comorbid migraine. It has been assumed that sleep disturbances are secondary to pain. A growing body of evidence suggests however, that insomnia can lead to or worsen pain. Data from clinical studies indicate that improving sleep may improve comorbid pain. Experimentally-induced sleep deprivation in healthy, pain–free humans leads to development of spontaneous pain, enhanced sensitivity to evoked pain, and decreased capacity to inhibit pain. Sleep deprivation also progressively deteriorates positive outlook and social functioning. A potential mechanism interconnecting sleep, pain, and mood may be inflammation.

Pain and Inflammation
Presenters in the third session addressed the roles of glial activation and bacteria in modulating pain, the impact of sleep-induced metabolite clearance from the brain, and neuroimmune mechanisms of depression and pain. Evidence was presented for the role of glial cells as “volume controllers” that are able to create and maintain an enhanced pain state via pro-inflammatory cytokines when triggered by neuropathy, other stressors, or opioids. Glial activation is also linked to opioid tolerance, dependence, withdrawal, and reward. Targeting glia and glial activation pathways is a novel approach to pain control, including increased opioid efficacy. Bacteria represent another unexpected means of enhancement of pain. Bacteria produce pain not by activating immune cells, as was historically assumed, but by directly activating nociceptors. Molecular waste products, including pro-inflammatory cytokines, are thought to be cleared via the pulsatile flow of cerebrospinal fluid (CSF) throughout the cortex during sleep. This process is disrupted however, in chronic pain, which may further exacerbate the pain. People with chronic pain may need more sleep to compensate for this diminished waste clearance. Inflammation-induced changes in both the spinal cord and the brain lead to activation of neurotransmitter pathways that in turn lead to mood dysregulation.

CONCLUSION

The biological, psychological, and social underpinnings of chronic pain must be better understood in to improve treatments and care for people with chronic pain and to prevent the transition from acute to chronic pain in those who are vulnerable. This symposium features recent research advances that will serve to guide future directions for pain researchers.
WORKSHOP SUMMARY

WELCOME AND OPENING REMARKS

The NIH Pain Consortium
Nora Volkow, M.D., Director, NIDA, NIH Pain Consortium Executive Committee Member

The mission of the NIH Pain Consortium is to enhance pain research and promote collaboration among researchers across the NIH ICs that support programs and activities addressing pain.

Dr. Volkow highlighted the following ongoing activities of the Pain Consortium:

- **Development of Clinical Research Resources**
  - Task Force on Research Standards for Chronic Low Back Pain (cLBP)
    The Task Force created a set of standard data elements and definitions to enhance and integrate data collection and outcomes reporting in clinical research on cLBP.
  - NIH and Stanford University Pain Registry
    Many existing registries are tied to the pharmaceutical industry and are not openly accessible for investigators. The NIH and Stanford registry is an open-source, centralized registry for self-reported information and over time, outcomes of chronic pain management. It was designed to address the dearth of data on persons with pain and long-term outcomes of chronic pain and its treatment.

- **Educational Tools**
  - Centers of Excellence in Pain Education
    The Centers of Excellence in Pain Education were designed to develop, evaluate, and distribute free pain management curriculum resources for medical, nursing, dental, and pharmacy schools to enhance and improve how health care professionals are taught about pain and its treatment.

- **Research and Discovery**
  - Interagency Pain Research Portfolio Database
The database, which was launched May 27, 2014, was developed as a publicly accessible resource that categorizes all federally funded pain research grants. More than 1,200 grants are entered into the database.

- **Opioids and Chronic Pain Workshop**
  This conference will take place on September 29 and 30, 2014 and will bring together experts to weigh evidence on the efficacy of opioids for chronic pain. There is very little data on opioids’ effectiveness in the management of chronic pain. The workshop will address the need to better understand issues such as indications for use of opioids for treating chronic pain and optimizing their use. A conference report will be published in January 2014.

**KEYNOTE ADDRESS**

**TRP Channels of the Pain Pathway: Connecting Physiology to Atomic Structure**

**David Julius, Ph.D., University of California, San Francisco**

Dr. Julius’s research focuses on understanding the process of nociception—how sensory (also called “primary afferent”) nerve fibers detect noxious stimuli. Primary afferent nerve fibers respond to a wide range of physiologic and environmental stimuli, through their membranes are embedded with ion channels or openings that allow substances to flow into the cell and transduce this information to the central nervous system (CNS). One such family of ion channels is called transient receptor potential (TRP) channels.

Although every cell in the body has TRP channels, not much is known about their functions and roles. Despite their ubiquity, no high-resolution (atomic) structural information existed previously to guide scientists’ understanding of what they look like, how they interact with other proteins, and how drugs interact with them. It is known that one type of TRP channel, called TRPV1, detects temperature and may convey the sensation of noxious heat by activating primary afferent fibers, which send the signal to the CNS.

TRPV1 channels are referred to as polymodal signal integrators, which means they can be acted on by a wide array of physiological and pharmacological stimuli, including heat, low pH, local tissue acidosis, and bioactive lipids such as anandamide and other endocannabinoids.

Dr. Julius’s team used cryo-electron microscopy (cryo-EM) to visualize the TRPV1 protein and study its structure using three-dimensional reconstructions.

The group found that the central pore of the channel through which ions flow has two restriction points and that both must open before ions can enter the cell. This structural element may explain why TRPV1 channels can be regulated by so many
physiological mediators: the two restriction points represent two regulatory pathways within the channel.

Dr. Julius’s team used ligands, substances that attach to the channel, such as capsaicin, resiniferatoxin, and tarantula venom (which keeps TRPV1 in the open state) to visualize and compare TRPV1’s structure in open versus closed states. These studies confirmed the location of the ligands’ attachment sites. The channel’s ligand-activated open state also showed that both restriction points are open when the ligands are attached. These analyses also revealed structure-function relationships of different parts of the channel, allowing the team to characterize how ligands prompt the channel to move to an open state and how it changes shape so that ions can flow through it.

The atomic structure provides a mechanistic view of how the channel is regulated by inflammatory mediators and provides insight into how drugs could be developed to target specific parts of the channel to act as analgesics. This work also can serve as a blueprint for understanding how other TRP channels may function in pain signaling.

An audience member asked about the role of ligands found naturally in the body. Dr. Julius explained that TRPV1 is activated by such substances including anandamide and other endocannabinoid derivatives. An audience member asked if TRPV1 heat signal processing occurs exclusively at the periphery. Dr. Julius said that TRPV1 is a heat sensor in the skin that sends a message about temperature to the CNS.

PANEL SESSION ON PAIN AND DEPRESSION

Moderator: Wendy B. Smith, M.A., Ph.D., BCB, Senior Scientific Advisor, OBSSR

Session Overview: Pain and Depression—What Exactly Is the Relationship?

Dan Clauw, M.D., University of Michigan

Studies suggest that the relationship between chronic pain and depression is bidirectional: each increases the risk of the other. The frequency with which pain and depression co-occur depends on many factors, including how they are measured and the nature of the populations studied. In general, all types of psychiatric disorders—not just depression—are more likely to occur when chronic pain is present.[10] Many other factors, such as early life stressors, other psychiatric conditions, prior pain, prior somatic symptoms, and poor sleep, are stronger than depression in predicting the development of chronic pain.[11, 12] Pain and depression both are triggered by stress, are processed by limbic brain structures [13, 14] and involve many of the same neurotransmitters. The two conditions however, have distinct neurobiological underpinnings Dr. Clauw suggested therefore, that our focus should move from depression as the most
important CNS comorbidity of chronic pain to viewing pain disorders as centralized pain syndromes.

Pain, psychiatric symptoms, fatigue, sleep disturbances, and memory problems are hallmarks of centralized pain syndromes, a term used here to include somatoform disorders, regional idiopathic pain syndromes (tension headache, irritable bowel syndrome, temporomandibular joint dysfunction [TMD], interstitial cystitis [IC], vulvodynia, dry eye disease), and fibromyalgia. They are called by different names but may be part of the same disease as they almost always co-occur. Centralized pain syndrome may be characterized as multifocal pain with higher lifetime history of pain, multiple other somatic symptoms, and sensitivity to multiple sensory stimuli.[15] It is not a “yes or no” disorder; it occurs over a wide continuum.

Previously, experts believed that fibromyalgia was a discrete illness characterized by focal areas of tenderness, negative psychological and behavioral factors, and chronic widespread pain. Now, scientists are beginning to view fibromyalgia as a continuum of symptoms, driven by common central changes that manifest as multiple somatic symptoms. In addition, psychological and behavioral factors play roles in only some individuals with fibromyalgia.

Centralized pain is one-and-a-half to two times more common in females, has strong familial/genetic underpinnings,[16] is triggered or exacerbated by stressors[15], and is characterized by generally normal physical examination except for diffuse tenderness and nonspecific neurological signs.[17]

Studies have shown that a person’s fibromyalgia score predicts pain intensity, symptoms, and disability over a wide range of musculoskeletal disorders, including rheumatoid arthritis, osteoarthritis (OA), regional musculoskeletal pain, and fibromyalgia [18]. Dr. Chad Brummett and Dr. Clauw are conducting a study of predictors of outcomes in OA patients undergoing total knee and hip replacements. Their primary hypothesis is that the measures of centralized pain (as measured by the fibromyalgia score) in OA will predict poor outcome after arthroplasty. Recent analyses showed that increased surgical site pain severity, neuropathic pain, anxiety, depression, catastrophizing, and use of home opioids were correlated with higher fibromyalgia scores. The increase in opioid use may indicate either more pain or reduced effectiveness of opioids in these individuals. Patients’ fibromyalgia scores were the strongest predictor of continued pain at six months post-surgery.[19]

Whereas depression is an important component, studies should consider the importance of other co-morbid symptoms and focus on the underlying pathogenesis of centralized pain. Some chronic pain results from a problem in the area of the body in which symptoms arise; other chronic pain is the manifestation of a lifelong disease characterized by centralized symptoms; most chronic pain falls somewhere between these two states.
Pain and Mood Regulation in Women with Chronic Pain
Mary Davis, Ph.D., Arizona State University

Emotion dysregulation is common in people with chronic pain. Recent research suggests that recruitment of resilience resources, which include positive social ties and positive affect, appear to improve both pain and mood.

In a recent study of women with fibromyalgia, Dr. Davis’s group found that a stressor (morning loneliness) predicted the emergence of negative emotions in the afternoon and pain in the evening. In subjects who had a resource in the form of positive social ties however, morning loneliness did not predict afternoon negative emotions and evening pain.[20] Thus, resilient people with solid positive social ties experience fewer negative effects from stressors.

In another recent study of women with fibromyalgia and/or OA, of whom 29 percent were depressed, Dr. Davis’s team induced stress in the subjects by asking them to talk about an ongoing social conflict in their lives. Depressed individuals who were given positive mood induction (a humorous film sample) and non-depressed individuals given either positive or neutral (an educational film sample) mood inductions were able to recover their jovial mood after the stressor whereas depressed individuals given the neutral mood induction did not recover. Pain increased during the stressor, then decreased following the mood induction for all groups, except for the depressed individuals given neutral mood induction, whose pain did not significantly decrease after mood induction.[21]

CBT is the most widely used behavioral treatment for chronic pain but it does not focus on bolstering positive emotional and social relationships in order to elicit resilient responses to pain and stress. Mindfulness approaches help patients regulate their responses to pain and stress and boost positive affect. In a randomized trial comparing CBT, mindfulness, and a control treatment in patients with rheumatoid arthritis and recurrent depression, those given mindfulness treatment improved more in positive affect and pain coping and decreased more in negative affect, catastrophizing, fatigue, disability, and joint tenderness and swelling than did individuals in the two other groups.[22]

In a study comparing an online mindfulness intervention with a control intervention in fibromyalgia patients, pain did not change across groups, negative affect improved in both groups, and positive affect, social activity, family enjoyment, loneliness, and pain coping efficacy improved in the mindfulness group.[23]

In summary, resilient responding in chronic pain patients can be bolstered by targeting emotion regulation, especially by boosting resilience resources. The mindfulness acceptance–based approach led to improvements in positive affect and social engagement and dampened pain and stress reactivity.
Psychosocial Influences on Pain and Depression
Courtney DeVries, Ph.D., Ohio State University, College of Medicine

Dr. DeVries’ research examines the physiological mechanisms through which psychosocial factors alter the risk of chronic pain and affective disorders after nerve injury.

In one of her studies, 14 days of stress (restraint) exacerbated hypersensitivity to touch and depressive-like behavior in animal models of nerve injury. Corticosterone (a marker of stress) increased to a greater extent in nerve-injured animals than in sham animals exposed to stress. Interleukin-1 beta gene expression (a marker for cortical inflammation) also increased in nerve-injured mice exposed to stress, suggesting that nerve injury increases neural inflammation in the cortex, and exposure to stress following injury exacerbates the effect. When corticosterone synthesis was blocked chemically before restraining the animals, corticosterone levels and cortical IL-1 beta expression did not increase in response to the stressor indicating that blocking corticosterone alters the inflammatory response to stress. The block also ameliorated the effects of stress on hypersensitivity and depressive-like behavior after nerve injury. Blocking IL-1’s function prior to restraint prevented depressive-like behavior in the nerve-injured mice suggesting that nerve injury enhanced neuroinflammation through IL-1 beta expression, contributing to depressive-like behavior.

Social interaction in the form of pair-housing prior to nerve injury reduced development of hypersensitivity and depressive-like behavior. Social pairing after nerve injury also reduced hypersensitivity, suggesting that it is possible to reverse the effects even after injury has occurred. Social interaction however, did not eliminate the effects of stress on hypersensitivity in nerve-injured animals. It appears therefore, that IL-1 beta plays a role in mediating the effects of social interaction on hypersensitivity.

In summary, nerve injury causes neuroinflammation, which in turn promotes the development of depressive-like behavior. Stress exacerbates neuroinflammation, hypersensitivity, and depressive-like behavior through a corticosteroid-mediated pathway. Social interaction reduces these negative effects of nerve injury.

Panel Session Q&A

An audience member asked Dr. Clauw to comment on the role of a peripheral generator in driving central pain. Dr. Clauw responded that peripheral generators can indeed drive central sensitization, but that targeting periphery generators will not be effective in altering central sensitization in everyone who develops it. An audience member asked about the risk for depression in patients who first develop chronic pain in middle age. Dr. Davis noted that people with recurrent depression are more vulnerable to precipitants of all kinds, including stress and chronic pain,
but those with no history of depression do not necessarily develop pain-associated depression. Dr. DeVries was asked whether social interaction could reduce allodynia after long-term centralized pain. Dr. DeVries believes such an outcome is possible and is currently testing this hypothesis.

INTRODUCTION TO THE JUNIOR INVESTIGATOR PRESENTATIONS

Gayle E. Lester, Ph.D., Program Director, NIAMS

NIH junior investigators invited to present posters at this meeting are supported by NIH fellowships, career development awards, or their first independent investigator research grant. Three posters were selected as particularly outstanding. Each of these three poster presenters gave oral presentations with the most exceptional one selected to receive the Mitchell Max Award for Research Excellence, an award that has been presented annually since 2009 to honor Dr. Mitchell Max for his lifetime contribution to pain research.

Neural Mechanisms Supporting Mindfulness-Based Pain Relief as Compared to Placebo Analgesia
Fadel Zeidan, Ph.D., Wake Forest School of Medicine

Mindfulness meditation appears to improve anxiety, depression, mood, pain, and other health outcomes.[7, 9, 25-28] Dr. Zeidan’s group used brain imaging to look at how mindfulness meditation alters brain responses to painful heat.

Participants were given mindfulness meditation training, placebo, sham mindfulness meditation or book listening (control).

Whereas, placebo, sham, and mindfulness interventions all reduced pain intensity and unpleasantness somewhat, mindfulness meditation was most effective at reducing these measures. Mindfulness meditation alone significantly reduced activation of the thalamus, a region of the brain that relays sensory information and the periaqueductal gray, which is involved in modulating pain perception. The effects of meditation in attenuating pain appear to occur through multiple mechanisms. Placebo also may engage in modulating processes in the brain, whereas the sham meditation–related pain relief may have also occurred in part through relaxation-related mechanisms. The clinical efficacy of brief meditation appears to be almost immediate and may prove to be attractive to clinicians, patients, and health insurers to treat pain.

In response to a question about his interpretation of periaqueductal gray activation, Dr. Zeidan stated that orbitofrontal cortex and other prefrontal cortex regions may be inhibiting lower-level brain regions and thalamus; therefore, the deactivation of the periaqueductal gray may represent a gating mechanism associated with a cognitive reappraisal approach to the noxious experience. Dr. Zeidan stated that
there were no differences in pain expectation between the meditation and sham groups.

**Identification of TMD Subtypes: The OPPERA Study**

Eric Bair, Ph.D., University of North Carolina at Chapel Hill, School of Dentistry

TMD is an orofacial pain disorder that is centrally mediated in many, but not all, people. It is a heterogeneous condition with many possible causes. Optimal treatment may depend on the characterization of subsets of patients.

To identify TMD subsets, Dr. Bair’s group performed cluster analyses on data from the Orofacial Pain Prospective Evaluation and Risk Assessment Study (OPPERA), a prospective cohort study of TMD. The study population includes 1,031 chronic TMD cases and 3,247 initially TMD-free controls. Of these controls, 260 developed TMD during a three-year follow-up period.

Using measurements of psychological distress and pain sensitivity, three putative clusters of subgroups were identified: Cluster 1: low pain sensitivity and low psychological distress; Cluster 2: low psychological distress and higher pain sensitivity; Cluster 3: high psychological distress and high pain sensitivity. Earlier work by Dr. Bair’s group indicated that these measures represent risk factors for developing TMJ and are driven by genetic and environmental factors. [29, 30] Cluster 1 contained the lowest proportion of people who developed TMD, whereas Cluster 3 contained the highest proportion. Orofacial pain, other pain, jaw dysfunction, and co-occurring conditions were low in Cluster 1, intermediate in Cluster 2, and highest in Cluster 3, indicating that Cluster 3 consisted of patients with more severe forms of TMD. In the TMD-free individuals, those from Cluster 3 had higher hazard ratios for first-onset TMD at follow-up.

Future research will involve development and validation of methods to identify individuals who will develop TMD and eventually to tailor treatment in accord with risk for progressing to a chronic pain disorder.

**Resting State Alterations in Women with Interstitial Cystitis/Painful Bladder Syndrome**

Lisa Kilpatrick, Ph.D., University of California, Los Angeles, David Geffen School of Medicine

IC/painful bladder syndrome (PBS) is a female-predominant chronic pelvic pain condition associated with urinary urgency and frequency and pain, which may affect more than 7 million women in the United States.[31] The specific pathophysiology is thought to involve a central disturbance in the processing of pain and viscerosensory signals in the brain.[32]
Using resting state functional imaging (fMRI), techniques, Dr. Kilpatrick’s group explored differences in brain activity and connectivity across cortico-cerebellar sensory motor networks associated with bladder dysfunction, in the brains of women with IC/PBS compared to those of healthy controls.

Sensorimotor regions of the cortex are involved in pelvic floor muscle control, and the red nucleus of the midbrain is a supraspinal center connected to the bladder, which serves as a relay station between sensorimotor cortex and the cerebellum. Compared with healthy women, the brain scans showed that IC/PBS patients showed alterations in oscillation dynamics of neural activity and connections across areas of the brain that process viscero-sensory, somatosensory, and motor information. The altered activity is thought to reflect increased neural activity that tonically increases viscero-sensory input into the brain. Decreased connectivity across certain brain regions suggests reduced integration of interoceptive information into subjective awareness. The increased oscillation frequency observed in the sensorimotor cortices may reflect altered neural activity in these regions in patients; alternatively, it also might reflect a greater contribution of blood-oxygen-level dependent (BOLD) signaling in deeper cortical layers in the patients. In addition, connectivity changes between sensorimotor cortices and the midbrain were greatest in patients experiencing pain during bladder filling.

The alterations in viscero-sensory regions in IC/PBS patients may reflect tonically increased viscero-sensory input to the brain and altered integration of interoceptive information into subjective awareness. These results suggest that women with IC/PBS have structural and functional alterations in cortico-cerebellar pathways previously associated with bladder and pelvic floor function.

UPDATE FROM THE AMERICAN PAIN SOCIETY

The American Pain Society Research Agenda
Roger B. Fillingim, Ph.D., University of Florida

The American Pain Society (APS) believes that improving the relief of pain can be achieved by collaborative approaches to interdisciplinary research, education, treatment, and advocacy. The goal of the American Pain Society's research domain is to have NIH and other funders recognize pain as a distinct and high-priority health care problem that deserves increased resources for research.

The APS collaborates closely with the NIH PC to help disseminate funding opportunities to its members and to advocate for increased pain research funding. Since 2005, the APS has awarded more than $1.8 million in grants to junior emerging research leaders through its award programs, which include:

- Young Investigator Travel Support
A new initiative for the APS is the Pain Research Fund, which provides a mechanism for members and non-members to donate funds to the APS to support future research grants.

The APS currently is developing a white paper that presents a research agenda and goals for pain research in the 21st century. These goals include:

- **Goal 1:** Develop novel pain treatments that enhance clinically meaningful pain relief and functional improvement with no or clinically acceptable adverse effects.
- **Goal 2:** Expedite progress toward the prevention, diagnosis, and management of chronic pain conditions.
- **Goal 3:** Optimize the use of and access to currently available treatments that are known to be effective.
- **Goal 4:** Understand the impact and influence of health policies and systems on pain treatment.
- **Goal 5:** Improve pain management through education and research.

The overall goal of APS's research agenda is to address the entire research perspective, with the ultimate aim of reduced pain in the population.

**PANEL SESSION ON PAIN AND SLEEP DISORDERS**

**Moderator:** Ann O'Mara, Ph.D., RN, FAAN, Head of Palliative Care Research, NCI

**Genetic Basis of Chronic Pain**

**William Lariviere, Ph.D.,** University of Pittsburgh

Studies of twins, families, and inbred mouse strains have established that pain sensitivity and pain disorders are heritable and influenced by genetic alterations.[33, 34] One of the first genes to be associated with pain was catechol-O-methyl transferase (COMT), which may affect pain through dopaminergic modulation of opioid systems. COMT activity also is associated with psychiatric traits, including depression.

In addition to COMT, a number of other pain-related genes associated with neurotransmitter systems and ion channel function have been identified, including melanocortin 1 receptor mu-opioid receptor 1, and GTP cyclohydrolase 1. Many of the pain-related genes also are associated with analgesia and its side effects. Many challenges are associated with the study of genetic associations with pain, including:
• Conflicting findings occur: for example COMT has been associated with both positive and negative aspects of nearly all pain conditions.[35]
• Specificity for type of pain is mostly lacking in the pain genetics literature. The type of pain associated with COMT varies across species (i.e., COMT is associated with the rate of temporal summation of heat pain in humans and with acute inflammatory pain in rodents[29, 36]).
• The selection of candidate genes often is not determined objectively for example, by interrogating chromosomal loci data, gene expression changes in animal models, automated protein pathway searches, and automated keyword searches of the literature.[37] Interrogated data should be genome-wide and made publicly available.

Dr. Lariviere emphasized the need for more big data studies to generate convergent and objective findings. These datasets should be analyzed and re-analyzed as additional datasets and analysis techniques emerge. There is also a need to conduct more systematic meta-analyses and to place a single gene's results in the larger context of systems neurogenetics.

**Genetic Basis of Human Clock and Links to Migraine**

**Louis Ptacek, M.D., University of California, San Francisco**

Migraine affects 10 to 15 percent of the population and is highly heritable. However, the mode of heritability is unclear. Genetic studies of familial migraine syndromes have identified associated mutations in a number of ion channel genes.

Circadian rhythm and sleep play an important role in human health and disease, and disruptions increase the risk for problems with metabolism, obesity, immunity, learning and memory, mood disorders, migraine, and cancer. Dr. Ptacek and colleagues recently began studying the genetics of familial sleep-wake phenotypes, including people with advanced sleep phase (“morning larks”), delayed sleep phase (“night owls”), and natural short sleep. Familial advanced sleep phase (FASP) is an autosomal dominant trait where people fall asleep early and wake early. Underlying mutations have been identified in the Per2 and CK1d genes.[38] In one FASP family, all six carriers of the T44A mutation in the CK1d gene (which was shown to be the causative mutation of FASP in drosophila and mouse models) also have asthma and migraine with aura. Subsequently, a second family was identified with FASP and migraine with aura and a CK1d mutation.

Given the association between migraine and the T44A mutation in the CK1d gene, Dr. Ptacek's group induced the mutation in mice. They found that compared to wild type mice, the mutant mice had decreased thresholds for cortical spreading depression and increased arterial dilation and sensitivity to peripheral allodynia, all of which are features of migraine.[39]
In another FASP family, the affected members are short sleepers (six to six-and-a-half hours) and have severe depression and anxiety. Studies on mice with the same genetic mutation showed that mice had shortened sleep periods, as well as depressive-like behavior. The affected family members responded well to treatment of depression and anxiety. When the mouse mutants were tested with the same drugs, their sleep periods returned to normal and they displayed reductions in depressive-like and anxiety-like behavior.

The Effects of Cognitive Behavioral Therapy for Comorbid Insomnia and Pain
Michael V. Vitiello, Ph.D., University of Washington

Chronic pain often co-occurs with sleep disturbances. One approach to treat chronic pain therefore, may be to treat the sleep problems, rather than the pain itself.

In a re-analysis of data from a prior study, Dr. Vitiello’s group found that CBT for insomnia (CBT-I) improved both sleep and pain in older adults with OA and insomnia. Improving sleep in these patients may be “analgesic.” The likely reciprocal effects of pain dysfunction and sleep disturbance offer a compelling rationale for integrated management of these disorders.[40]

A subsequent randomized controlled trial in older adults with comorbid OA and insomnia compared the effectiveness of CBT targeting both arthritis pain and insomnia (CBT-PI) to standard CBT targeting pain alone (CBT-P) and a pain and sleep education-only control. Over nine months, CBT-PI significantly improved insomnia and sleep efficiency relative to the control intervention. CBT-PI also improved insomnia relative to CBT-P, and both improved sleep efficiency compared to the control intervention. Pain severity was not significantly reduced by any of the interventions.[41] Further analysis showed that although insomnia treatment effects were attenuated over time, they were greater for both sleep and pain outcomes in persons receiving the combination CBT-PI intervention. In a subgroup of participants who had both severe pain and severe insomnia symptoms at baseline, the benefits were greater than for that of the overall cohort [42]. Furthermore, regardless of treatment condition, subjects whose sleep improved by 30 percent or more experienced sustained improvement in insomnia, sleep quality, fatigue, pain severity, and arthritis symptoms.[43]

The overall findings suggests that successful treatment of sleep disturbance in OA with comorbid insomnia may yield benefits for reduced pain over the long term, contingent on achieving robust and sustained improvements in sleep.

The Effects of Sleep Disruption on Pain and Mood: Role of Inflammatory Markers
Monika Haack, Ph.D., Harvard University
Dr. Haack's group has conducted a number of experimental sleep studies in healthy participants without histories of mood or pain-related disorders. Her team found that prolonged sleep restriction progressively deteriorates positive outlook and social functioning [44] and increases spontaneous pain. Her group subsequently looked at effects of repeated periods of restricted sleep, with intermittent catch up periods of full sleep. Pain habituation (adaptation to pain) is diminished in subjects who undergo these restriction protocols. Habituation to stressors or other challenges is a key protective feature of many biological systems, but with repeated exposure to sleep restriction, the ability to habituate to cold pain deteriorates.

Sleep has a regulatory influence on all major physiological systems, many of which affect pain processing and vice versa including the opioid, monoaminergic, stress, and inflammatory systems. The inflammatory process is a mechanistic pathway likely linking sleep dysfunction and pain. Inflammatory markers (IL-6 and prostaglandin E2) increase across repeated episodes of sleep restriction and deprivation and do not return to baseline after periods of full sleep. Similar correlations of IL-6 levels occur with spontaneous pain episodes. [45], [46]

Sleep deficiency, in an experimental or natural setting, leads to development or facilitation of spontaneous pain, enhanced sensitivity to evoked pain, and decreased capacity to inhibit pain and to habituate to pain. Inflammatory mediators, such as IL-6 and prostaglandin E2, appear to play a role in mediating these features of sleep deficiency and pain.

Panel Session Q&A

Dr. Vitiello was asked to elaborate on CBT-I. He explained that the therapy involves time-in-bed restriction, stimulus discrimination therapy, sleep hygiene, and cognitive reframing. In contrast, CBT-P involves behavioral activation and relaxation. The panel members were asked about ethnic differences in their studies; they noted that insufficient subjects to date and geographical distribution preclude meaningful analyses. The panel members discussed the relationship between sedatives, sleep disorders, and pain, which they conclude needs exploration.

Dr. Vitiello discussed nighttime pain; in his studies, OA subjects improved on a measure of sleep-related pain. Dr. Haack elaborated on her group’s subject recruitment process, which requires people to be monitored over two weeks and to demonstrate healthy, high-quality sleep before enrollment. During the study, sleep-monitoring equipment confirms that subjects slept the designated amount of time.

In response to a question on sleep’s effects on inflammatory factors and pain, Dr. Haack cited her finding that hypertensive participants who slept one hour longer over a six-week period had drastic decreases in blood pressure and non-significant decreases in stress markers. This finding however, points to acute effects and chronic effects of sleep deprivation may be different, involving central mechanisms.
rather than inflammation. Dr. Vitiello agreed that it takes a while for pain to
decrease with improved sleep, suggesting that acute and chronic effects use
different mechanisms.

MITCHELL MAX AWARD FOR BEST JUNIOR INVESTIGATOR PRESENTATION

Patricia A. Grady, Ph.D., RN, FAAN, Director, NINR, NIH Pain Consortium Executive
Committee Member

The NIH PC recognizes the importance of supporting early-stage investigators and
highlighting the work of those investigators. Mitchell Max was not only devoted to
pain research, but he was also very committed to the training of young investigators.
The three junior investigator presentations were judged by a panel of Pain
Consortium member scientists from across the NIH. They selected the top finalist
based on the quality of the presentation, the innovative nature of the research, and
the depth of knowledge of the presenter. Each year, selection of the recipient of the
award is very difficult, and as in the past, all three of this year's presenters are
deserving of recognition. The 2014 Mitchell Max Best Junior Investigator
Presentation Awardee is Dr. Fadel Zeidan.

A PATIENT’S PERSPECTIVE

Cynthia Toussaint, For Grace

Thirty-two years ago, Ms. Toussaint was a 21-year-old ballerina, singer, and actress
when a minor injury in her leg triggered a chronic pain disease called complex
regional pain syndrome (CRPS). She described the pain as though her leg had been
doused in gasoline and lit on fire. She was forced to stop dancing and often had to
crawl to get around. Her care giver performed all daily activities, such as cooking,
cleaning, grocery shopping, and laundry.

The pain eventually spread to both legs and she needed additional care. Her doctors
told her that her problems were all in her head even as her condition worsened.

Toussaint spent the next decade of her life bedridden. For five of those years, she
was unable to speak as the CRPS spread through her body and ravaged her vocal
cords. After losing her career, friends, and independence, she devised a suicide plan,
because of the constant pain and fatigue.

In 1997, Toussaint gained access to a multidisciplinary pain clinic, where she first
received a diagnosis of CRPS. The diagnosis allowed for her to receive appropriate
medications, physical and psychological therapy. Toussaint began to recover.
Soon after, Toussaint founded For Grace to raise awareness about CRPS. After learning about the disparities in occurrence and treatment of chronic between men and women in pain she expanded For Grace’s mission to ensure the adequate and equal treatment of all women in pain.

In 2011, Toussaint experienced a second partial CRPS remission in which she regained her ability to participate in aerobic exercise, to fully use her hands and arms, and to walk short distances.

She related that overtreatment lead to exacerbation of her condition.

Since then, however, Toussaint has recovered and improved by practicing self-care, with meditation; biofeedback; singing; exercising; healthy eating, drinking and sleeping.

Toussaint closed by emphasizing the importance of pain research to provide hope for people suffering from chronic pain. These people are counting on the knowledge gained from research so they can prove their pain is real, understand its causes, and receive better treatments and ultimately, a cure.

The question-and-answer session included comments from clinicians who treat chronic pain. One noted hurdles with authorization from health insurers for medications used for chronic pain. Another clinician commented that water therapy may be helpful.

A RESOURCE FOR PAIN RESEARCH

The Stanford-NIH Pain Registry

Collaborative Health Outcomes Information Registry (CHOIR): Open Source Platform for Measuring Health Outcomes
(Formerly ‘Health Electronic Registry of Outcomes’ – HERO)
Sean Mackey, M.D., Ph.D., Stanford University

The IOM reported in Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research, that more consistent data on pain are needed, in part through patient outcome registries.[3]

The CHOIR, developed by Dr. Mackey, addresses this need. The goal was to develop an open source, highly flexible, health and treatment registry. The registry is used to collect outcomes data on large numbers of patients suffering from chronic pain and other health conditions. It will enable point-of-care decision-making; software-based decision-making (e.g., learning-based systems); comparative-effectiveness
and longitudinal research; large, simple trial designs; and practice-based evidence trials.

CHOIR features easy-to-use data entry screens for patients and clinical staff, workflow support, point-of-care reporting to support clinical decision-making, and data import support for automated data entry for medications and other treatments, medical conditions, costs, and other elements.

CHOIR is a flexible platform that allows for surveys on clinical conditions, including an extensive Pain CHOIR survey. It uses industry-standard tools and no commercial vocabulary or proprietary libraries. It also uses NIH’s Patient-Reported Outcomes Measurement Information System (PROMIS) computer adaptive testing (CAT) surveys and legacy instruments. CHOIR ties in with clinic scheduling, and automated email software sends reminders to patients to fill out the surveys, which can be done at home on personal computers, tablets, or smartphones.

CHOIR was rolled out in 2012 and now has over 3,500 unique patients and over 10,000 longitudinal data assessments.

The providers use the instruments frequently for teaching and decision-making. For example, in CHOIR’s computer-assisted documentation feature, patient-reported history components are displayed according to the provider’s needs for documentation. The system also tracks dynamic outcomes of individual subjects. In the research domain, CHOIR allows for comparison of the pain clinic population’s pain and psychometric properties to the population. This feature allowed Dr. Mackey to leverage knowledge about the Stanford pain population to create a better-optimized version of the survey system, further decreasing the number of survey questions patients must answer. Large-scale analysis of measures has revealed distinct patient subgroups. It has also allowed Stanford researchers to study the dynamics of psychological processes.

The team continues to develop and optimize CHOIR, adding practice-specific modules, more sophisticated software, expanded integration with other platforms, consolidation of data, integration of genetic information, and more patient-friendly access. The future of CHOIR also involves collaborations to expand it to multiple clinics and academic centers. Dr. Mackey and colleagues are providing the source code with minimal licensing requirements and are looking for partners to help add features. He hopes that CHOIR will ultimately help change health care nationwide.

The question-and-answer session touched on CHOIR’s ability to pull information examinations from electronic health records. Dr. Mackey also explained that while patients cannot directly access data they submit, providers may share paper reports with patients.
Scientists increasingly are recognizing the role of non-neuronal players in development and maintenance of persistent pain—namely, glia in the spinal cord and trigeminal nucleus.

Microglia survey the CNS and rapidly respond to challenge by releasing neuro-excitatory, pain-enhancing substances. These actions, particularly the release of pro-inflammatory cytokines, amplify both pain signaling to the spinal cord and pain transmission to the brain, enhancing pain and opposing opioid analgesia. A variety of substances activate this glial response, including danger signals (that indicate cell stress, damage, and death), opioids, and cocaine. Animal studies indicate that spinal glial activation opposes both morphine and methadone analgesia.

Opioid-like substances (agonists and antagonists) can affect neurons and glia differently because neuronal opioid receptors are sensitive to the structural orientation of substances that attach to them, whereas glial opioid receptors are not. Thus, (+)-naloxone’s structure allows it to bind to glia and not neurons. Naloxone blocks the activity of its target and attenuates morphine’s effectiveness by acting on glia to reduce their activation rather than by directly acting on neurons. This feature suggests that opioid effects on glia and neurons may be separable, which may allow for reducing the side effects and improving the efficacy of opioids by structurally modifying them to prevent glial activation or by creating a long-lasting version of (+)-naloxone to only block glia.

The glial receptor that detects (+)-naloxone is Toll-like receptor 4 (TLR4) that detects bacterial products, danger signals, and clinical opioids. Opioid-induced constipation is decreased in TLR4 knockout mice and by (+)-naloxone. Further, (+)-naloxone (TLR4 antagonist) reverses neuropathic pain as well as neuropathy-induced glial activation in animals. (+)-Naloxone also inhibits reward.

These data predict that blocking glial and subsequent immune activation will suppress neuropathic pain and opioid, tolerance, dependence, reward, and other adverse side effects.
Several therapeutic compounds are approaching clinical trials. One potential therapeutic is non-viral gene therapy (called XT-101, from Xalud Therapeutics) to induce release of IL-10, an anti-inflammatory cytokine to reverse neuropathic pain and glial activation. A single intrathecal injection of XT-101 in rodents reverses nerve injury- and chemotherapy-induced neuropathic pain for 3 months.[55-57] XT-101 is also successful in pet dogs with chronic pain.

In summary, glial cells enhance development and maintain persistent pain. Glial activation is also linked to opioid tolerance, dependence, withdrawal, and reward. Targeting glia and glial products may provide a novel approach to pain control and may increase opioid efficacy.

**Bacteria Activate Sensory Neurons That Modulate Pain**

**Clifford Woolf, M.D., Ph.D.,** Boston Children’s Hospital

The classic view of nociceptors is that they detect potentially harmful chemical, mechanical or thermal stimuli and transduce pain signals as a protective warning device. The immune cells that are present at the site of tissue damage and inflammation produce pro-inflammatory immune mediators and cytokines that activate nociceptors. The concept of pathogens directly interacting with nociceptors however, has not been extensively explored. Scientists assumed that pathogens interact only with immune cells, which then release mediators that activate sensory neurons, but these views have been challenged.[58]

Dr. Woolf’s lab found that injection of live bacteria into the hindpaw of mice produced pain hypersensitivity. Subsequent microscopic examination showed bacteria in close proximity to the nociceptors, but not to immune cells. Peak bacterial load coincided with the peak of pain hypersensitivity, but not with the time at which immune cells peaked, suggesting direct effects of bacteria on nociceptors. Furthermore, calcium imaging revealed that heat-killed bacteria placed into culture selectively activated subsets of sensory neurons—in this case, only TRPV1-expressing, capsaicin-responsive neurons.

Bacteria produce formyl peptides, and nociceptors contain receptors for formyl peptides. Exposure of nociceptors to formyl peptides produced pain hypersensitivity, which was attenuated in genetically engineered mice with inactivated formyl peptide receptors, indicating that bacterial formyl peptide is at least one way bacteria activate sensory neurons.

These results indicate that bacteria produce pain not by activating immune cells, but by directly activating nociceptors through secreted formyl peptides and alpha-hemolysin.[59]

**Sleep Drives Metabolite Clearance from the Brain**

**Maiken Nedergaard, M.D.,** University of Rochester
The CNS is a metabolic, highly active system and it produces waste that must be recycled or disposed. CSF may act as a sink for this waste, and pulsatile flow of CFS through the brain may wash out waste products.

Dr. Nedergaard’s lab used in vivo and ex vivo imaging of CSF tracers to show that it rapidly enters the brain along the vasculature, then spreads throughout the cortex. These CSF fluxes propel the waste products of neuron metabolism into the paravenous space, from which they are directed into lymphatic vessels and ultimately return to the general circulation for clearance by the kidney and liver. This system has been dubbed the “glymphatic system.”

Dr. Nedergaard’s group used electrocorticography (ECoG) to demonstrate that arousal regulates glymphatic activity such that CSF flow into the brain increases during sleep and decreases during wakefulness. In waking states, CSF flows more readily into the spinal cord rather than the brain. Mice with pain induced by spared nerve injury (SNI) demonstrated a low influx of CSF into the brain during sleep relative to a high flow of CSF into the spinal cord, resembling an extremely wakeful state. Mice with SNI that are given ketamine anesthesia have an increase in CSF flow into the brain.

These results suggest that in pain states, the brain is not adequately clearing waste via CSF influx. People with chronic pain may need longer sleep periods in order to compensate for diminished waste clearance. The glymphatic system may also be important for clearing proinflammatory cytokines and chemokines, which are involved in maintenance of pain. If so, the glymphatic system may play a role in modulating pain. Glymphatic flow ultimately might be used as a tool to diagnose pain levels.

**Neuro-Immune Mechanisms of Depression and Pain**

**Annemieke Kavelaars, Ph.D.,** University of Texas, M.D. Anderson Cancer Center

Comorbid chronic pain and depression may be regulated by a common neuroimmune mechanism. The current model posits that inflammation, nerve damage, cancer therapy, and related factors can activate both the nervous and immune systems. The immune system then produces inflammatory mediators that signal changes in inflammatory responses and neurotransmitter signaling (through tryptophan metabolism) in the brain. These interactions then affect behavior, contributing to symptoms of fatigue, depression, cognitive deficits, and pain.

Treatment of hepatitis C patients with the cytokine interferon 1-alpha causes increases in neurotoxic tryptophan metabolites and depression scores.[60] IDO1, a tryptophan metabolizer, also plays a crucial role in inflammation-induced depression-like behavior and hyperalgesia in mice.[61, 62] Thus, a large inflammatory response leads to increased circulating cytokines as well as a signal in
the brain that activates IDO, which metabolizes tryptophan, leading to depression-like behavior.

In chronic neuropathic pain patients, however, there is not a large increase in circulating cytokines. Dr. Kavelaars’s group wondered whether this pathway is activated in chronic pain. In mouse models of neuropathic pain, the cytokine IL-1 is released in the spinal cord. Blocking IL-1 signaling in the spinal cord reduced both mechanical hyperalgesia and depression-like behavior. In genetically engineered mice without IDO1 pain induced depression-like behavior was diminished, but pain behavior was not. The mice did not have increased expression of IDO1 in the brain and spinal cord. It was increased however, in the liver, and there were increases in brain enzymes and metabolites of tryptophan. In addition, blocking IL-1 signaling in the brain prevented expression of tryptophan/kynurenine metabolizing enzymes and metabolites in the brain and liver and diminished depression-like behavior but did not affect pain behavior. Blocking the kynurenine metabolizing enzyme KMO inhibited depression-like behavior but not pain.

In the presence of chronic neuropathic pain, which occurs in the absence of high levels of systemic inflammation, inflammation-induced depression takes place. Pain appears to cause the release of IL-1 in the brain, inducing the liver to express the enzyme that initiates tryptophan metabolism, and the brain to up-regulate an enzyme that further processes the product of tryptophan metabolism, ultimately leading to depression-like behavior.

**Panel Session Q&A**

In response to a question about whether blocking the toll-like receptor with naloxone creates vulnerability to infection, Dr. Watkins noted the redundancy of the immune system, which has many other mechanisms to compensate for vulnerability. Dr. Watkins currently is looking at ways to reverse glial priming; several mediators appear to be able to do this.

Dr. Woolf elaborated on the effect of the local inflammatory response on nociceptors, which he believes is less important in the acute phase. One could surmise that bactericides may be analgesic. Formyl peptides and alpha-hemolysin probably represent just two of many bacterial components that affect pain. Dr. Woolf explained that expression of an adaptor protein in the recipient cell membrane is required for achieving specificity with the alpha-hemolysin. In response to a question about how the small number of bacteria-responsive nociceptors accounts for such a robust behavioral effect, Dr. Woolf replied that heat-killed bacteria in culture lack alpha-hemolysin and contain only the formyl peptide, and that the *in vitro* experiments are simply model systems to tease out mechanisms and do not actually represent what happens *in vivo* with live bacteria.
Dr. Nedergaard acknowledged that neurocilia probably play a role in CSF flow and waste removal. Dr. Kavelaars speculated that a direct neuronal pathway exists by which IL-1 beta in the brain signals to the liver.

**CLOSING REMARKS AND ADJOURN**

**Josephine P. Briggs, M.D.,** Director, NCCAM, NIH Pain Consortium Executive Committee Member

Dr. Briggs stated that this is a good time for pain research at NIH. Besides basic science, strengthening clinical pain research is an important priority. A crucial resource that has entered the funding arena is the Patient-Centered Research Outcomes Institute (PCORI). She emphasized the importance of ensuring that pain research is “PCORI-ready,” so that large-scale clinical studies can be carried out.

Dr. Briggs’ team at NCCAM is leading the Health Systems Collaboratory, which is developing methods for conducting large-scale pragmatic trials using health care systems. Two Collaboratory projects are pain-related.

Another resource for pain research is the recently published report of the trans-NIH task force on research standards for cLBP (report available on the NIH PC website, [www.painconsortium.nih.gov](http://www.painconsortium.nih.gov)). The task force consisted of 16 experts in all clinical domains affected by pain. The manuscript describing the report has been published in multiple journals.

Finally, the IPRP Database recently was released ([paindatabase.nih.gov](http://paindatabase.nih.gov)). The database provides information on all federally funded pain research and training activities. It is intended to strengthen oversight of pain research and the ability to build bridges between different areas of pain research.

Dr. Briggs concluded by thanking the participants in the Pain Consortium symposium and expressed her enthusiasm for continuing the dialogue in the future.
APPENDIX 1: AGENDA

9th Annual NIH Pain Consortium Symposium on Advances in Pain Research
Biological and Psychological Factors that Contribute to Chronic Pain

Wednesday, May 28, 2014

8:30 a.m.  Welcome and Opening Remarks
Nora Volkow, M.D., Director, NIDA, NIH Pain Consortium Executive Committee Member

8:45 a.m.  Keynote Address
*TRP Channels of the Pain Pathway: Connecting Physiology to Atomic Structure*
David Julius, Ph.D., University of California, San Francisco

9:30 a.m.  Panel Session on Pain and Depression
Moderator: Wendy B. Smith, M.A., Ph.D., BCB, Senior Scientific Advisor, OBSSR
Session Overview: *Pain and Depression—What Exactly Is the Relationship?*
Dan Clauw, M.D., University of Michigan

10:10 a.m.  *Pain and Mood Regulation in Women with Chronic Pain*
Mary Davis, Ph.D., Arizona State University

10:30 a.m.  *Psychosocial Influences on Pain and Depression*
Courtney DeVries, Ph.D., Ohio State University, College of Medicine

10:50 a.m.  Panel Session Q&A

11:10 a.m.  Poster Session and Break in the Atrium

11:40 a.m.  Introduction to the Junior Investigator Presentations
Gayle E. Lester, Ph.D., Program Director, NIAMS
11:45 a.m.  *Neural Mechanisms Supporting Mindfulness-Based Pain Relief as Compared to Placebo Analgesia*

Fadel Zeidan, Ph.D., Wake Forest School of Medicine

12:00 p.m.  *Identification of TMD Subtypes: The OPPERA Study*

Eric Bair, Ph.D., University of North Carolina at Chapel Hill, School of Dentistry

12:15 p.m.  *Resting State Alterations in Women with Interstitial Cystitis/Painful Bladder Syndrome*

Lisa Kilpatrick, Ph.D., University of California, Los Angeles, David Geffen School of Medicine

12:30 p.m.  Lunch

1:30 p.m.  Poster Session in the Atrium

2:00 p.m.  Update from the American Pain Society

*The American Pain Society Research Agenda*

Roger B. Fillingim, Ph.D., University of Florida

2:20 p.m.  Panel Session on Pain and Sleep Disorders

Moderator: Ann O’Mara, Ph.D., RN, FAAN, Head of Palliative Care Research, NCI

*Genetic Basis of Chronic Pain*

William Lariviere, Ph.D., University of Pittsburgh

2:40 p.m.  *Genetic Basis of Human Clock and Links to Migraine*

Louis Ptacek, M.D., University of California, San Francisco

3:00 p.m.  *The Effects of Cognitive Behavioral Therapy for Comorbid Insomnia and Pain*

Michael V. Vitiello, Ph.D., University of Washington

3:20 p.m.  *The Effects of Sleep Disruption on Pain and Mood: Role of Inflammatory Markers*

Monika Haack, Ph.D., Harvard University

3:40 p.m.  Panel Session Q&A

4:00 p.m.  *Mitchell Max Award for Best Junior Investigator Presentation*

Patricia A. Grady, Ph.D., RN, FAAN, Director, NINR, NIH Pain Consortium Executive Committee Member

4:10 p.m.  Adjourn
Thursday, May 29, 2014

8:30 a.m.  A Patient’s Perspective

Cynthia Toussaint, For Grace

Introduction: Susan Marden, Ph.D., Program Director, NINR

8:50 a.m.  A Resource for Pain Research

The Stanford-NIH Pain Registry

Sean Mackey, M.D., Ph.D., Stanford University

Introduction: Susan Marden, Ph.D., Program Director, NINR

9:30 a.m.  Panel Session on Pain and Inflammation

Moderator: Catherine Bushnell, Ph.D., Scientific Director, Intramural Research, NCCAM

Panel Session Overview: Targeting Glial Activation for Treating Chronic Pain and Improving the Clinical Efficacy of Opioids

Linda Watkins, Ph.D., University of Colorado, Boulder

10:10 a.m.  Poster Session and Break

10:40 a.m.  Bacteria Activate Sensory Neurons that Modulate Pain

Clifford Woolf, M.D., Ph.D., Boston Children’s Hospital

11:00 a.m.  Sleep Drives Metabolite Clearance from the Brain

Maiken Nedergaard, M.D., University of Rochester

11:20 a.m.  Neuro-Immune Mechanisms of Depression and Pain

Anemieke Kavelaars, Ph.D., University of Texas, M.D. Anderson Cancer Center

11:40 a.m.  Panel Session Q&A
12:00 p.m.  Closing Remarks and Adjourn

Josephine P. Briggs, M.D., Director, NCCAM, NIH Pain Consortium
Executive Committee Member
APPENDIX 2: LIST OF POSTERS

1. Identification of TMD Subtypes: The OPPERA Study
   Eric Bair, Sheila Gaynor, Luda Diatchenko, Gary Slade, Shad Smith, Roger Fillingim, Joel Greenspan, Ron Dubner, Richard Ohrbach, William Maixner
   University of North Carolina at Chapel Hill

2. Treatment of Chronic Pain and Opioid Dependence with Buprenorphine and Counseling: Rationale and Study Design
   Declan T. Barry, Richard S. Schottenfeld
   Yale School of Medicine

3. Factors Associated with Opioid Overdose Death Among Older Adults Prescribed Opioids
   Amy S.B. Bohnert, Deborah A. Levine, Dara Ganoczy, Yun Chen, Iquo Nafiu, Frederic C. Blow
   University of Michigan

4. Optogenetically Modulating Pain Pathways Using uLED Devices
   Daniel S. Brenner1,2, Gunchul Shin3, Tae-il Kim4, Sung Il Park3, Vijay Samineni2, John A. Rogers3, Robert W. Gereau IV2
   1Medical Scientist Training Program, Washington University School of Medicine; 2Pain Center and Department of Anesthesiology, Washington University School of Medicine; 3Department of Materials Science and Engineering, Frederick Seitz Materials Research Laboratory, University of Illinois at Urbana-Champaign; 4School of Chemical Engineering, Sungkyunkwan University

5. Task-Negative Network Dysfunction in Fibromyalgia Patients Is Related to Lack of Modulation by Cognitive Load
   Marta Čeko, John L. Gracely, Mary-Ann Fitzcharles, David A. Seminowicz, Petra
6. **Tonic Inhibition of Latent Central Sensitization by Mu Opioid Receptor Constitutive Activity**

   **Suzanne Doolen,** Gregory Corder, Bradley K. Taylor

   University of Kentucky

7. **Developing Gene Therapy for Pain—HSV Vectors Targeting Gene Expression to Selected Sensory Neuron Subtypes**

   **Mark F. Doyal**¹, Mingdi Zhang¹, William F. Goins¹, Tsuyoshi Majima², Naoki Yoshimura³, Justus B. Cohen¹, Michael S. Gold³, Joseph C. Glorioso¹

   ¹Department of Microbiology and Molecular Genetics, ²Department of Urology, and ³Department of Anesthesiology, University of Pittsburgh School of Medicine

8. **Role of Mitochondrial Dysfunction in the Development of Periorbital Sensitivity in a Rat Model of Chronic Migraine**

   **Nathan T. Fried,** Michael L. Oshinsky

   Thomas Jefferson University

9. **Oxidized Lipid Agonists of TRPV1 Play a Role Mediating Pain in a Model of Partial-Thickness Burn Injury**

   **Dustin Green,** Shivani Ruparel, Linda Roman, Michael A. Henry, Ken M. Hargreaves

   The University of Texas Health Science Center at San Antonio

10. **Alterations in Resting State Oscillations and Connectivity within Sensory and Motor Networks in Women with Interstitial Cystitis/Painful Bladder Syndrome**

    **Lisa A. Kilpatrick**¹, Jason J. Kutch², Kirsten Tillisch¹, Bruce Naliboff¹, Jennifer Labus¹, Zhiguo Jiang¹³⁴, Melissa Farmer⁵, A. Vania Apkarian⁵, Sean Mackey⁶, Katherine T. Martucci⁶, Dan Clauw⁷, Richard E. Harris⁷, Georg Deutsch⁸, Timothy
11. Urologic Symptoms of a Subset of Urologic Chronic Pelvic Pain Syndrome (UCPPS) Patients with a Poly-Symptomatic, Poly-Syndromic Pattern of Presentation—A MAPP Research Network Study

H. Henry Lai1, Carol S. North2, Gerald L. Andriole1, Lori Cupps3, David Song1, Timothy J. Ness4, Barry A. Hong3

1Division of Urologic Surgery, Department of Surgery, and 3Department of Psychiatry, Washington University School of Medicine; 2Departments of Psychiatry and Surgery/Division of Emergency Medicine, VA North Texas Health Care System and University of Texas Southwestern Medical Center; 4Department of Anesthesiology, University of Alabama at Birmingham

12. Blood-Based Pain Biomarkers for Bodily Pain and Headache in Military Service Members

Hyunhwa Lee

National Institute of Nursing Research, NIH

13. Molecular Targets of Dezocine and Their Clinical Implications

Renyu Liu1, Xi-Ping Huang2, Alexei Yeliseev3, Jin Xi1, Bryan L. Roth2

1Department of Anesthesiology and Critical Care, Perelman School of Medicine,
14. **Chronic Non-Resolving Nerve Injury in the Rat Causes Behavioral Changes and Global and Cellular Abnormalities in Brain Morphology**

   Lucie A. Low, Binquan Wang, Scott J. Thompson, M. Catherine Bushnell

   National Center for Complementary and Alternative Medicine, NIH

15. **Longitudinal Evaluation of Taxane-Induced Neuropathy in Early-Stage Breast Cancer**

   M.B. Lustberg, S. Monfort, J. Singaravelu, X. Pan, A. Chaudhari

   1Stefanie Spielman Comprehensive Breast Center, Division of Medical Oncology, Department of Internal Medicine; 2Departments of Orthopaedics and Biomedical Engineering; 3Center for Biostatistics; and 4School of Health & Rehabilitation Sciences and Department of Mechanical and Aerospace Engineering, The Ohio State University

16. **A Critical Role for Src in Phosphoregulation of TRPV1 Activity by PKC: Implications for Metastatic Bone Cancer Pain**

   A.D. Mickle, A.J. Shepherd, R.A. Merrill, L. Loo, S. Strack, D.P. Mohapatra

   Department of Pharmacology, Carver College of Medicine, University of Iowa

17. **A Principle Neurotransmitter, Nppb, and Its Role in Itch Sensation**

   Santosh Mishra

   National Institute of Dental and Craniofacial Research, NIH

18. **The Moderating Effect of Sleep Fragmentation on the Association of Sleep Duration and Pain in Adults with Sickle Cell Disease**

   Gyasi Moscou-Jackson, Patrick Finan, Claudia M. Campbell, Jennifer A. Haythornthwaite
19. **Ictal Adipokines Are Modulated by Pain Severity and Acute Treatment Response in Episodic Migraineurs**

N. Cindy Chai, Bizu Gelaye, Gretchen E. Tietjen, Paul D. Dash, Barbara A. Gower, Linda W. White, Thomas N. Ward, Ann I. Scher, B. Lee Peterlin

1Department of Neurology, Johns Hopkins University School of Medicine; 2Department of Epidemiology, Harvard School of Public Health; 3Department of Neurology, University of Toledo; 4Department of Neurology, Johns Hopkins Community Physicians; 5Department of Nutrition Sciences, University of Alabama at Birmingham; 6Department of Neurology, Dartmouth Hitchcock Medical Center; 7Uniformed Services University of the Health Sciences

20. **Voluntary Exercise and Weight Control Attenuate Nociceptive Hypersensitivity in a Rat Model of Rheumatoid Arthritis**

M.H. Pitcher, I.Z. Rauf, M.C. Bushnell

National Center for Complementary and Alternative Medicine, NIH

21. **Cyclin-Dependent Kinase 5 Modulates Orofacial Mechanical and Thermal Pain**

Michaela Prochazkova, Bradford Hall, Anita Terse, Ashok B. Kulkarni

Functional Genomics Section, Laboratory of Cell and Developmental Biology, National Institute of Dental and Craniofacial Research

22. **Effect of Interleukin-10 (IL-10) and Weight on Intestinal Permeability Test Solution Response**

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23. **Peripheral Proprioceptive and Central Nociceptive Responses to Spinal Manipulation Dosage Parameters**

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24. High Morphine Equivalent Opioid Prescription and Duration of Use Are Associated with Increased Risk of Depression

Jeffrey F. Scherrer, Patrick J. Lustman, Sumitra Balasubramanian, Joanne Salas, F. David Schneider, Sandra Burge

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25. Illness Representations and Catastrophizing as Predictors of Abdominal Pain in Adults with Irritable Bowel Syndrome

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26. The Responsive Amygdala: Treatment-Induced Alterations in Functional Connectivity in Pediatric Complex Regional Pain Syndrome

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27. Bortezomib Alters Microtubule Polymerization and Axonal Transport in Rat Dorsal Root Ganglion Neurons

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28. **Finding Good TEMPOS with the SAX: Preliminary Definitions of Temporal Postoperative Pain Signatures via Symbolic Aggregate Approximation**

   **P.J. Tighe, P. Rashidi, P. Nickerson, R. Fillingim**

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29. **Optogenetic Activation of a Corticostriatal Circuit Inhibits Both Sensory and Depressive Symptoms of Pain**

   **M. Lee, T. Manders, S. Chen, J. D’Amour, S. Eberle, R. Froemke, J. Wang**

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30. **Modulation of Visceral Pain by Interaction Between Adrenergic Receptors and TRPV4**

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31. **Adherence in African Americans Being Treated for Cancer Pain**

   **Katherine A. Yeager**

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32. **Neural Mechanisms Supporting Mindfulness-Based Pain Relief as Compared to Placebo Analgesia**

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