



This symposium focused on mechanisms and management of overlapping chronic pain and associated conditions. The presentations covered three major areas:

- Neurological mechanisms that may contribute to comorbid pain conditions.
- Psychosocial factors that may contribute to pain conditions.
- Treatment strategies and obstacles to managing overlapping pain conditions.

Introduction and Welcoming Remarks

Nora D. Volkow, M.D., Director, National Institute on Drug Abuse (NIDA), and Pain Consortium Co-Chair

Dr. Volkow described the National Institutes of Health (NIH) Pain Consortium and reviewed research and education gaps in chronic pain management. The NIH Pain Consortium was established in 1996 to coordinate pain-related activities across NIH. Five NIH Institute and Center (IC) directors serve as the consortium's executive committee and 24 ICs participate in its activities.

In the United States, 75 million people suffer from pain, and its consequences can be devastating. Although effective interventions are available for acute pain, this is much less true for chronic pain. Meta-analyses, for example, show that opioid analgesics, the most frequently used chronic pain treatment, are less effective for chronic than acute pain.

Although the total number of prescriptions for opioid analgesics in the United States has risen steadily over the past two decades, significant numbers of patients still do not receive appropriate pain management. Furthermore, pain medications are the main cause of overdoses, and the number of unintentional drug overdoses has increased five-fold since 1990. One reason why so many opioids are prescribed inappropriately and so many patients do not receive the pain treatment they need is lack of education on pain for health care providers.

Update on NIH and the Patient Protection and Affordable Care Act

Isabel Garcia, D.D.S., M.P.H., Acting Director, National Institute of Dental and Craniofacial Research (NIDCR), and Pain Consortium Co-Chair

Dr. Garcia described the pain-related provisions of the Patient Protection and Affordable Care Act that the Pain Consortium is helping implement. The first of these activities was to ask the Institute of Medicine (IOM) to address the current state of the science in pain research, care, and education and explore approaches to advance the pain field. The IOM has now formed the Committee on Advancing Pain Research, Care, and Education, which has collected public testimony from a broad group of stakeholders. The committee will deliver a pre-publication report to Congress by June 30, 2011.

The Act also directed the Pain Consortium to develop and submit recommendations on pain research initiatives to the NIH Office of the Director for support by the NIH Common Fund, which supports projects that can transform health research by overcoming barriers or filling knowledge gaps. The Consortium has issued a call for proposals and the Executive Committee will meet shortly to review the proposals and decide which ones to forward for potential Common Fund support.

In response to a third provision of the Act, NIH is establishing an interagency pain research coordinating committee to identify critical research gaps, stimulate pain research collaborations, and provide an important venue for public involvement in the pain research agenda. NIH has solicited recommendations for potential committee members to the Secretary of Health and Human Services, who will appoint the committee members.

Overview of the American Pain Society's Evidence-Based Clinical Guidelines

Mark Jensen, Ph.D., American Pain Society Member and Editor in Chief of the Journal of Pain

Dr. Jensen provided an update on American Pain Society (APS) activities and APS's clinical guidelines for pain. APS offers annual scientific meetings, publishes *The Journal of Pain* and evidence-based guidelines, and supports new investigators and clinical centers of excellence. APS has issued guidelines on several pain-related topics, including, most recently, on using chronic opioid therapy in chronic non-cancer pain. The goal of these guidelines is to promote the implementation of evidence-based clinical care. APS is now developing guidelines on methadone safety and on postoperative pain.

Neurological Mechanisms that May Contribute to Comorbid Pain Conditions

Moderator: *David Thomas, Ph.D., NIDA*

Modulation of Central Neuroplasticity: Central Nervous System (CNS) Hypersensitivity in Chronic Pain States

Robert Gereau, Ph.D., Washington University

Dr. Gereau discussed potential mechanisms of debilitating chronic pain syndromes. Patients often have more than one form of chronic pain, such as fibromyalgia and migraine. Many underlying and coexisting pain conditions are not consistent with identifiable peripheral or spinal mechanisms, such as tissue damage or infection. Some researchers have therefore speculated that comorbid pain conditions are due to amplification of pain within the CNS.

Studies have shown that metabotropic glutamate receptor 5 (mGlu5) is a key mediator of pain-related plasticity at several sites in the nervous system, including the periphery, spinal cord, and amygdala. Dr. Gereau has studied the role of the amygdala, a forebrain structure, in mediating

pain sensitization that extends beyond the site of injury. In particular, he has examined the ERK signaling pathway, which is activated in neurons and other cells.

Several studies have involved formalin (painful) or saline (non-painful) injections into the hind paw of a mouse and measurements of the animal's subsequent pain behavior and sensitivity to touch in the injured paw and the contralateral, uninjured paw. These studies showed that mGlu5 activation in the amygdala's central nucleus mediates a form of ERK-dependent central sensitization that can increase pain sensitivity at loci that are far removed from the injury site. This neural substrate could play a role in chronic pain comorbidities.

Spontaneous Brain Dynamics in Chronic Pain: New Challenges

Dante Chialvo, M.D., Brentwood Biomedical Research Institute

Dr. Chialvo discussed the impact of chronic pain on cortical dynamics. Studies show that the brain shuts down certain resources and activates others when people without chronic pain are paying attention to a trivial task. When patients with chronic back pain perform the same trivial tasks, the brain activation and deactivation patterns are very different. In these patients, the medial prefrontal cortex stays activated and their activation/deactivation balance is disrupted. Even when patients with chronic back pain are not doing anything, their brains show enhanced interactions between the insular cortex and the default mode network. These regions of the brain are not related to pain but they do play a role in attention and emotions.

A novel method, resting bold evoked triggered average (rBeta), uses spontaneous BOLD fluctuations to monitor interactions among brain regions. This approach can be used to measure spontaneous or induced inter-subject variability. Research shows, for example, that rBeta reveals altered interactions in key brain areas in patients with fibromyalgia compared to healthy patients. In addition, the rBeta of patients with fibromyalgia correlates with clinical parameters, including scores on the Beck Depression Inventory.

Amplified Pain Responses in Persistent Inflammatory Pain Conditions

Gayle Page, D.N.Sc., R.N., Johns Hopkins University

Dr. Page provided evidence from animal studies that sleep restriction enhances the mechanical sensitivity that results from sciatic inflammatory neuritis (SIN) and paclitaxel, a chemotherapeutic drug for solid tumors and lymphoid cancer. Dr. Page's laboratory infused zymosan from yeast cell walls into Gelfoam around the sciatic nerve in Sprague Dawley rats. The rats were kept awake for 6 hours after lights went on for 10 days. Sleep restriction and zymosan infusions in the left hind paw reduced paw withdrawal thresholds and increased mechanical sensitivity. However, the combination of zymosan and sleep restriction did not reduce paw withdrawal thresholds more than either intervention alone. Male and female animals showed sensitivity in the right hind paw, but male animals showed significantly less hypersensitivity than females after zymosan and sleep restriction.

When Dr. Page and her colleagues used a similar experimental design but injected paclitaxel instead of zymosan, the animals that received the paclitaxel injections only showed sensitivity in

the injured paw, but those with restricted sleep were even more sensitive. Paw withdrawal thresholds decreased progressively during the 7-day rest periods between cycles, but recovery was lower after each cycle and was even lower in sleep-disturbed animals.

Towards Mechanisms of Sleep Disruption Hyperalgesia

Michael Smith, Ph.D., Johns Hopkins University

Dr. Smith discussed the relationship between sleep disturbance and pain processing. He has used the diffuse noxious inhibitory controls (DNIC) paradigm, in which pain inhibits pain, to study the mechanisms of sleep disturbance-induced hyperalgesia. Healthy participants were randomly assigned to forced awakening for 20 minutes every hour, restricted sleep (4 hours of uninterrupted sleep each night), or normal sleep for 7 nights and then put their hand into a circulating ice water bath. The results showed that sleep fragmentation, but not sleep restriction, impairs the endogenous pain inhibitory processes. Dr. Smith theorized that endogenous opioids moderate DNIC in part and sleep disruption or deprivation might alter this opioid system.

Another study included patients with myofascial temporomandibular joint disorder, a chronic pain disorder. DNIC measured as a percentage increase in pressure pain threshold during a cold pressor task was lowest in participants with the lowest sleep efficiency (those who slept less than 85% of the time when they were trying to sleep) and was highest in patients with sleep efficiency higher than 90%.

Attention and the ability to engage the cortex can modulate pain, and sleep deprivation might impair people's ability to distract themselves from pain. For example, people who have slept for 6.5 hours or less per night during the previous month demonstrate significantly less distraction analgesia when playing video games after exposure to heat-capsaicin cream (a model of neurogenic hyperalgesia) on the hand. They also have more skin flare and secondary analgesia in the form of hypersensitivity beyond the treated skin.

Panel Question-and-Answer Session

In response to a question about using deep brain electrical stimulation to manage severe chronic pain, Dr. Thomas explained that trans-cranial brain stimulation is used primarily as a research tool. However, the procedure is simple and safe and has been used to manage pain in some cases. This avenue is worth exploring.

A participant asked whether Dr. Smith had been surprised that the sleep-restricted participants in his study had not shown any changes in DNIC. Dr. Smith replied that this result was not surprising and was probably due to some characteristic of sleep-continuity disturbance. However, Dr. Smith was surprised that the forced-wakening group showed a robust loss of DNIC. He cautioned that this study was small and included only very healthy women, and the results do not mean that sleep restriction is beneficial. More research is needed to identify the aspects of sleep that are hyperalgesic.

When asked about using drugs to induce prolonged sleep to treat illness, Dr. Smith reported that he is unaware of evidence showing that hypersomnia could prevent or treat pain. Furthermore, sleeping more than 7.5 hours a night tends to have negative consequences.

A participant asked Dr. Gereau to discuss ERK activation in the right amygdala versus both sides of the amygdala. Dr. Gereau replied that in his studies, regardless of the paw that received the injury, ERK activation always occurred in the left amygdala. Activating ERK in the right amygdala results in bilateral hypersensitivity, whereas activating ERK in the left amygdala results in contralateral but not ipsilateral hypersensitivity. Some data suggest that mGlu5 expression is about 50% higher in the right than the left amygdala. Dr. Gereau is now trying to determine the mechanism for this effect, whether it is circuit based, and which receptors are expressed.

A participant asked each presenter to identify one lesson from his or her research for primary care physicians who treat chronic pain. Dr. Gereau said that pain is a very complex nervous system disorder and treating the peripheral mechanisms of pain is not sufficient. Dr. Page emphasized the importance of sleep in managing pain. Dr. Smith added that primary care providers need to ask their patients about their sleep.

A participant commented that the literature suggests that peripheral mechanisms and the central sensitization that takes place at many places in the CNS play an important role in pain. Blocking the peripheral nervous system eliminates the central sensitization and, thus, pain. Dr. Gereau replied that, in most cases, the peripheral drive initiates pain and eliminating peripheral input can prevent or reverse established chronic pain.

A participant asked whether stimuli that initiate sleep disturbance in patients with chronic pain are due to one fiber type. Dr. Smith replied that studies show that duration and intensity are important. Research also shows that the amount of thermal stimulation required to wake someone from sleep is equivalent to daytime pain tolerance.

Psychosocial Factors that May Contribute to Comorbid Pain Conditions

Moderator: *John Kusiak, Ph.D., NIDCR*

Impact of Early-Life Trauma on Adult Pain Sensitivity and Responsiveness to Stress

Anne Murphy, Ph.D., Georgia State University

Dr. Murphy discussed the effects of trauma during the perinatal period on adult somatization. In animal studies, carrageenan injections result in paw edema for 12–72 hours but, by 96 hours, the behaviors of injected and non-injected pups are indistinguishable and injured animals have a normal adolescence. After 60–90 days, females injured at birth do not withdraw their injured paw from a thermal stimulus for 16 seconds, compared to 12 seconds for injured males and 8 seconds for non-injured animals. Adult animals injured on the day of their birth also show

hyperresponsiveness to any perturbation. These results suggested a broad change in CNS somatization.

Naloxone produces a shift in somatosensation, indicating that early injuries change the endogenous opiate tone. Animals given naloxone reverse the injury-induced hypoalgesic response and the effects appear to be centrally mediated. The upregulation in endogenous opioid peptide expression that takes place in animals injured shortly after birth occurs within the midbrain periaqueductal gray. Animals injured at birth also show altered stress- and anxiety-related behaviors.

Effects of Early-Life Experiences: Modeling and Reinforcement

William Whitehead, Ph.D., University of North Carolina, Chapel Hill

Dr. Whitehead discussed the impact of social learning on the development of irritable bowel syndrome (IBS), a common gastrointestinal disorder that is associated with abdominal pain. In an analysis of data from a large health maintenance organization, children whose parents had IBS had significantly more health visits; higher outpatient health care costs; and health care visits for diarrhea, abdominal pain, or other gastrointestinal symptoms than other children. Data from a twin registry showed that IBS rates were higher in monozygotic twins than dizygotic twins of IBS patients. However, the proportion of dizygotic twins with IBS who had mothers with IBS was greater than of dizygotic twins with IBS who had co-twins with IBS. These results suggested that social learning or a shared environmental process contribute at least as much to the clustering of IBS within families as genetics.

A proof-of-concept study exposed children with chronic functional abdominal pain to the water load symptom provocation task, which induced visceral discomfort. Parents of these children participated in a short training session that provided no instructions or taught them to express sympathy for their child's somatic distress or to change the topic of discussion. Directing parents to pay more attention to their children's somatic complaints increased the number of complaints, whereas the children of parents who distracted them had fewer somatic complaints. In a subsequent study, children who received CBT and social learning showed greater decreases in pain and gastrointestinal symptom severity than children who received nutrition education only. In addition, parents taught to decrease attention to somatic complaints and redirect talk to positive achievements reported greater decreases in their child's pain than parents in the control group.

Sex Difference in Pain Responses and Susceptibility to Multiple Persistent Pain Conditions

Emeran Mayer, M.D., Ph.D., University of California, Los Angeles

This presentation focused on sex-related differences in pain sensitivity in people with gastrointestinal disorders and interstitial cystitis. Women are more likely to have persistent pain disorders, possibly because of differences in pain sensitivity between men and women. However, animal studies have yielded inconsistent results regarding sex-related differences in somatic and visceral pain.

The spontaneous pain experience is heavily modulated by emotional and cognitive factors. Some of the biological endophenotypes for this complex symptom-based syndrome are more common in women. Dr. Mayer hypothesized that this is related to modulation by factors other than nociceptive input and that these differences primarily reflect differences in endogenous pain modulation and not in organ sensitivity or sensitivity of ascending visceral afferent pathways.

Worst case prediction (or catastrophizing) is an endophenotype that is one of the strongest predictors of chronic pain severity and is more common in females. Nociceptive response does not explain the pain that people experience before exposure to a painful stimulus. Dr. Mayer's studies show that most sex differences occur in the emotional arousal circuit while the patient is expecting pain. Furthermore, acute or uncertain expectations of pain yield different responses in the brains of patients with IBS and healthy patients. Control subjects deactivate certain brain regions when expecting a stimulus but patients with IBS activate the efferent network of the brain.

Effects of Catastrophizing and Depressive Symptoms on Pain and Pain Management

Jennifer Haythornthwaite, Ph.D., Johns Hopkins University

Dr. Haythornthwaite described the relationship between pain-related catastrophizing and clinical pain. The key dimensions of pain-related catastrophizing are negative emotions (anxiety, depression, and rumination), attention to pain (magnification, exaggeration, and hypervigilance), and beliefs about pain (threat, helplessness, and pessimism). People who catastrophize show elevation and progression of the cortisol response in response to pain. High catastrophizing levels in otherwise-healthy young adults combined with exposure to pain can produce depressive symptoms. In addition, catastrophizing and depressive symptoms correlate with increased pain following total knee replacement.

Research using topical capsaicin cream combined with heat showed that early changes in catastrophizing were a good predictor of changes in pain when the temperature on the hand increased. However, changes in pain were not good predictors of catastrophizing. These studies showed that people respond to pain by catastrophizing, which contributes to pain amplification. Other studies show higher serum interleukin-6 levels in high catastrophizers than low catastrophizers after exposure to pain, and this relationship is independent of pain ratings. These results show that pain is stressful in high catastrophizers.

Panel Question-and-Answer Session

A participant asked whether panel members assessed or controlled for sleep history in the studies they described. Dr. Haythornthwaite replied that the findings she reported are independent of sleep. Moreover, the correlation between catastrophizing and sleep is low, although they share some features. Dr. Mayer's and Dr. Whitehead's studies did not control for or assess sleep, although the new NIH chronic pain consortium is studying sleep.

In response to a question about CBT and catastrophizing, Dr. Haythornthwaite reported that a substantial amount of evidence shows that catastrophizing is amenable to change by CBT.

However, without interventions, catastrophizing levels do not change. Dr. Mayer noted that many people with high catastrophizing levels also respond to placebo. Dr. Haythornthwaite explained that helplessness plays a major role in catastrophizing, and patients who catastrophize might believe that although they are helpless on their own, a drug can make a difference.

A participant suggested that research explore whether adolescents who self-mutilate experienced early-life trauma.

A participant asked whether Dr. Murphy had determined whether the sex differences she observed are due to an effect of the testosterone produced embryologically in the gonad on the androgen receptors or conversion of testosterone to estrogen. Dr. Murphy said that studies to answer this question are challenging because the procedures to “masculinize” females or “demasculinize” males would produce pain. Ideally, she would block the embryological surge of testosterone in utero by administering an inhibitor to the mother. She is seeking a less invasive approach to study the embryological surge in testosterone.

Poster Award Presentation

Patricia A. Grady, Ph.D., R.N., FAAN, Director, National Institute of Nursing Research, and Pain Consortium Co-Chair

Dr. Gracy awarded the 2011 NIH Pain Consortium Mitchell Max Award for Research Excellence to Dayna Loyd of the University of Texas Health Science Center at San Antonio for her poster, “Serotonin Enhances Proinflammatory Peptide Release from Rat and Human Trigeminal Nociceptors.”

Treatment Strategies and Obstacles to Managing Overlapping Pain Conditions

Moderator: *Linda Porter, Ph.D., National Institute of Neurological Disorders and Stroke*

Development and Evaluation of Non-pharmacological Treatments of Chronic Pain in Persons with Physical Disabilities

Mark Jensen, Ph.D., University of Washington

Dr. Jensen discussed interventions that target pain generators in the brain in people with physical disabilities. When people who experience pain imagine that their pain is being relieved or undergo hypnosis for pain relief, functional magnetic resonance imaging (fMRI) shows changes in the brain. A randomized controlled trial compared 10 sessions of self-hypnosis or electromyographic biofeedback in patients with spinal cord injury and chronic pain. Both interventions significantly reduced pain intensity but chronic daily pain dropped significantly and stayed low only after hypnosis.

Dr. Jensen is currently using electroencephalograms (EEGs) to evaluate the associations between the brain activity resulting from non-pharmacological pain treatments and pain. Participants are undergoing one session of hypnosis, meditation, transcranial direct stimulation (tDCS), EEG

biofeedback, and sham tDCS. Preliminary results from 19 subjects, including 12 who have completed all of the procedures, indicate that the interventions did not show the expected association between pain and brain wave activity. The interventions did alter brain activity but each intervention had a different effect. With meditation and hypnosis, for example, patients with increased alpha and decreased theta activity reported more pain relief, as expected. But with biofeedback, patients with decreased alpha and increased beta activity reported the most pain relief.

A Translational Pathway for Pain and Symptom Treatment in Cancer

Charles Cleeland, Ph.D., University of Texas, M.D. Anderson Cancer Center

This presentation addressed the use of a National Cancer Institute translational pathway for developing treatments for cancer-related pain, which affects hundreds of thousands of patients every year. Cancer-related pain often results in treatment changes or stoppage, potentially affecting patient survival.

Progress along the translational pathway varies by type of cancer pain. For example, good animal models are available for bone pain, researchers have explained many molecular mechanisms, and several existing and potential treatments (including orthopedic interventions, radiation therapy, and osteoclast inhibition) are now available. Animal models are only available for some components of chemotherapy-induced neuropathy, however, and no mechanistically based treatments have been developed. Furthermore, most novel therapy development programs have focused only on the painful component of chemotherapy-induced neuropathy and have not addressed the non-pain sensorimotor components that might be more disabling than pain.

Finally, no animal models and few treatments are available for aromatase inhibitor-induced arthralgias, and a mechanistic understanding of this type of pain is lacking. Clinical trials are currently investigating the use of acupuncture, androgen therapy, blue citrus, and glucosamine and chondroitin to treat arthralgias in patients with cancer. Potential mechanisms that need further research include depletion of estrogen in aromatase-inhibitor-induced arthralgias, bone loss, and anti-nociceptive effects through opioid pain fibers.

Strategies and Hurdles in the Management of Abdominal Pain in Adolescents

Eva Szigethy, M.D., Ph.D., University of Pittsburgh

Dr. Szigethy discussed neurobiological substrates for visceral pain in adolescents and strategies for treating visceral pain. Abdominal pain in IBD has been linked to degree of inflammation, motility, disease location, and strictures. More than 80% of adults and 35% of youths with inactive or mildly active IBD experience disabling abdominal pain. In a large ongoing study, Dr. Szigethy showed that the total pain score in children aged 9–17 with Crohn's disease correlates with symptom severity and depression, and pain frequency correlates with depression. A model containing anxiety, depression, and diarrhea predicted 30% of variance in self-reported total abdominal pain.

Dr. Szigethy is collecting neuroimaging data on children with depression, IBD, both, or neither. Preliminary data show that IBD-related words selectively change brain metabolism in the inferior frontal cortex in children with IBD and depression compared to negative and neutral words. In particular, the rostral anterior cingulate cortex, which processes emotions, shows decreased activity in children with depression or with depression and IBD. Furthermore, children with active IBD and pain have more cuneus activity, reflecting more visual processing and reliving of negative experiences associated with IBD-related words.

Eight to 12 sessions of CBT significantly reduce depressive severity in children with IBD and this effect lasts for at least a year. CBT also improves brain functioning and quality of life, decreases depression and abdominal pain, and produces a more optimistic illness narrative. Psychopharmacological agents might be effective in children whose symptoms do not respond to CBT.

New Approaches to Analgesia Involving TRPV1 Agonists and Allosteric Modulators

Michael Iadarola, Ph.D., NIDCR

Dr. Iadarola discussed approaches to analgesia using transient receptor potential V1 (TRPV1) antagonists, allosteric modulators, and agonists. TRPV1 is found in the tips of the nerves that sense nociceptive stimuli, including heat and acid. Many TRPV1 antagonist studies had to be terminated or suspended because the compounds produced hyperthermia or loss of heat pain sensation throughout the body. These results suggested the need to use TRPV1 antagonists for a short period of time and in a controlled environment, such as a hospital.

To block the nociceptive information and prevent the adverse effects associated with TRPV1 antagonists, Dr. Iadarola used an allosteric modulator of the TRPV1 receptor to enhance calcium influx into the cell, potentially producing a long-lasting analgesic effect. However, the terminal regains its sensitivity within a few days, so Dr. Iadarola is currently using high-throughput screening to identify additional allosteric modulators of TRPV1.

When TRPV1 agonists are administered intrathecally, they permanently cut the connection between the body and spinal cord, although the effects of peripheral administration are transient. These agonists use calcium overload to produce a highly selective lesion of pain fibers or neurons. Resiniferatoxin (RTX), a TRPV1 agonist, reduced pain substantially in a 23-year-old male with advanced renal cancer whose analgesia medications were no longer therapeutic. RTX essentially clamps only the axons that make TRPV1 in the dorsal root, affecting only the chronic pain and not sensations of heat or vibration. A Phase I clinical trial of intrathecal RTX for intractable pain is currently recruiting patients.

Panel Question-and-Answer Session

A participant wondered whether “coping” is the right word to use when discussing the analgesic effects of pain interventions because this word might give patients the impression that their pain cannot be controlled. Dr. Szigethy’s clinic is known as the “medical coping” clinic to destigmatize the clinic’s work. She tells patients that their disease has physical and emotional

components and comprehensive care requires addressing both components. In her experience, “coping” does not have negative connotations.

A participant asked Dr. Jensen whether he was able to distinguish spontaneous fluctuations in pain that might correlate well with EEG activity. Dr. Jensen explained that the slide showing no correlation in pain severity with EEG measures represented only baseline data from a single point in time. The slide showing significant associations came from several time points. Dr. Jensen plans to examine more data on changes over time and his studies will include more people who are not experiencing pain.

A participant asked whether the nerve might grow back more normally than in the pathological condition after a neuroma is removed by RTX. Dr. Iadorola said that when a neuron is cut back, the nerve does not necessarily grow back into the scar tissue but the resulting lesion can form another neuroma. The contribution of other axons that are regenerating is unknown.

In response to a question about how he decided to focus on RTX, Dr. Iadorola explained that his laboratory was examining cells that were ectopically expressing TRPV1 fused to green fluorescent protein, so the ion channel in the cell was visible. When the laboratory added capsaicin, the calcium increased without any deleterious effect. When the investigators added RTX, they saw a fragmentation of the endoplasmic reticulum and mitochondria and, eventually, dissolution of the cell membrane and nuclear membrane. These observations provided a basic science insight into how to use RTX clinically to target the lesion instead of trying to desensitize the receptor.

A participant asked about data on biological changes, such as in brain plasticity, from non-pharmacological interventions. Dr. Jensen replied that these data are not yet available but he plans to use fMRI and EEG studies to examine changes in brain density and mass and interrelationships.

Clinical and Translational Science Awards for Pain Research

Anne Willoughby, M.D., M.P.H., National Center for Research Resources

Dr. Willoughby described the NIH Clinical and Translational Science Award (CTSA) program, which provides an academic home for clinical and translational research. Each of the existing 55 CTSA sites receives \$4–20 million each year to support its programs. The total number of sites will grow to 60 this summer. More information on the CTSA program is available at www.ctsaweb.org.

Closing Remarks

Josephine Briggs, M.D., Pain Consortium Co-Chair, Director, National Center for Complementary and Alternative Medicine

Dr. Briggs reported that the National Center for Complementary and Alternative Medicine is developing an intramural branch or program focused on pain. The center is currently recruiting a leading pain investigator to head this new program. In addition, the NIH Patient Reported

Outcomes Measurement Information System (PROMIS) has developed a variety of tools and instruments to measure patient-reported outcomes that might be relevant to the kinds of research that participants in this symposium had discussed. Dr. Briggs encouraged participants to learn more about PROMIS by visiting its website, at <http://www.nihpromis.org/>. Dr. Briggs closed the meeting by thanking the symposium organizers and speakers.