DoD–NCCAM/NIH Workshop on Acupuncture for Treatment of Acute Pain

Emmeline Edwards, PhD,¹ Jean Louis Belard, MD, PhD,² John Glowa, PhD,¹
Partap Khalsa, DC, PhD, DABCO,¹ Wendy Weber, ND, PhD, MPH,¹ and Kristen Huntley, PhD¹

Abstract

The Department of Defense (DoD) and the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health (NIH) cosponsored a workshop that explored the possible benefits of acupuncture treatment for acute pain. One goal of the workshop was to establish a roadmap to building an evidence base on that would indicate whether acupuncture is helpful for treating active-duty military personnel experiencing acute pain.

The workshop highlighted brief presentations on the most current research on acupuncture and acute pain mechanisms. The impact of various modifiers (stress, genetics, population, phenotypes, etc.) on acute pain pathways and response to acupuncture treatment was discussed.

Additional presentations focused on common neural mechanisms, an overview of real-world experience with using acupuncture to treat traumatic acute pain, and best tools and methods specific for acupuncture studies. Three breakout groups addressed the gaps, opportunities, and barriers to acupuncture use for acute pain in military and trauma settings. Different models of effectiveness research and optimal research designs for conducting trials in acute traumatic pain were also discussed.

Introduction

ON FEBRUARY 2–3, 2011, the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health (NIH) and the U.S. Department of Defense (DoD) cosponsored a timely and important workshop, in Bethesda, Maryland, titled “Acupuncture Treatment for Acute Pain.” Josephine P. Briggs, MD, the NCCAM Director and Colonel Karl E. Friedl, PhD, the Director of the U.S. Army Telemedicine and Advanced Technology Research Center, highlighted the importance of developing multilevel approaches to symptoms management and treatment of pain in military populations. Emmeline Edwards, PhD, the Director of the NCCAM’s Division of Extramural Research, emphasized that the goal of the workshop was to explore the possible benefits of acupuncture treatment for acute pain and to establish a roadmap to building an evidence base to indicate if acupuncture is helpful for treating active duty military personnel who are experiencing acute pain. Acupuncture is currently used by some military physicians for treatment of military personnel in war theaters (i.e., Iraq and Afghanistan) and is frequently integrated in treating active-duty personnel

at selected clinics on military bases in the United States. These practices are components of a broader context of providing many complementary and integrated treatments for these personnel and for veterans. On Day 1 of the workshop, the presentations focused on the mechanisms of acute pain and summarizing the current evidence base on acupuncture for treating acute pain. On Day 2, the focus shifted to the most impactful next steps in acupuncture clinical research in military settings.

Invited participants included scientists with demonstrated expertise in pain, neuroanatomy and neurophysiology, mechanisms of acupuncture analgesia, and clinical studies and trials of acupuncture for acute and chronic pain; as well as clinicians who provide acupuncture treatment in military settings. The workshop roster of participants also included representatives from a number of NIH institutes and centers and relevant DOD agencies (see Appendix A).

Mechanisms and Neural Pathways of Pain

Ronald Dubner, DDS, PhD, Professor of Neural and Pain Sciences at the University of Maryland Dental School,

¹Division of Extramural Research, National Center for Complementary and Alternative Medicine (NCCAM), Bethesda, MD.

²Henry M. Jackson Foundation, Telemedicine and Advanced Technology Research Center, MCMR-TT, U.S. Army Medical Research and Materiel Command, Fort Detrick, Frederick, MD.

reviewed the mechanisms and neural pathways of pain. Dubner has contributed a large and important body of original research on pain processes over several decades. He indicated that major advances have been achieved in the following three areas: (1) sensory coding; (2) descending modulation; and (3) neuronal plasticity. These are all normal functions of the brain associated with injury. Their normal role is protective—to guard the injured site and let it recuperate and heal. Unfortunately, this protective and healing function sometimes goes awry such that changes in the CNS persist even after the peripheral-tissue injury response has resolved. A major challenge to future pain research is to understand the factors that contribute to the persistence of these changes and to develop interventions to attenuate their pathophysiologic effects. Dubner highlighted key findings within each area:

Sensory coding and neuronal plasticity

Sensory coding refers to the process by which the nervous system extracts stimulus feature information, such as intensity, quality, and duration from the environment. Since 1970, investigators have identified a number of receptors that innervate skin, muscle, and viscera, and that respond to tissue damage. These nociceptors respond to mechanical, thermal, or chemical stimuli. These stimuli are transduced into chemical and electrical energy by a process that leads to propagation of electrical impulses from the target tissues to the central nervous system (CNS). After injury, these receptors have increases in sensitivity and contribute to an increase in pain by peripheral sensitization. Another process, central sensitization, results in increased nociceptor activity leading to increased neuronal input to the CNS. The resulting functional changes in the spinal cord and brain ultimately amplify the sensation of pain.¹ In a similar fashion, nerve damage can also lead to increased activity in the nervous system except that, in this instance, sensitization begins at the damaged nerve and not in the tissue where the receptors are located. It appears that both tissue and nerve injury lead to prolonged hyperexcitability in the nervous system.

Under normal conditions, increases in noxious stimulation lead to increased pain sensation in the area of tissue damage. This characterizes the behavioral response to transient pain. There are two major characteristics of persistent pain following tissue or nerve injury. *Allodynia* can occur; that is, stimuli that are normally nonpainful will produce pain. These noxious stimuli also produce greater levels of pain after injury in the second condition, *hyperalgesia*.

After these injuries, central sensitization involves activation of glutamate receptors and other receptors that lead to plasticity (changes in structure and function) in the nervous system. For example, when a painful stimulus persists, activation of these receptors is ultimately thought to result in an influx of calcium into the cells and release of calcium from intracellular stores. Calcium is important for activation of different protein kinases in cells, resulting in an increase of receptor phosphorylation. The N-methyl-D-aspartate (NMDA) receptor is the best-characterized receptor in this process. Phosphorylation of the NMDA receptor is a major factor in central sensitization and the subsequent hyperalgesia. Changes in receptor-channel kinetics enhance the responsiveness of the receptor to synaptically released glu-

tamate and increase synaptic strength. This amplification of the response also increases sensitivity to subsequent stimulation, and results ultimately in allodynia and hyperalgesia. The use of cloning/molecular techniques has provided new insight into the cellular changes that occur in response to injury and the role of feedback from the CNS on these changes.

Sensory modulation

Brainstem descending pathways constitute a major mechanism for controlling pain transmission and modulating persistent pain.² In addition to the roles of peripheral neurons and intrinsic and projection neurons in the spinal cord, there is a third component of spinal-cord involvement in central sensitization mechanisms. This component involves descending input from supraspinal sites in the brainstem and forebrain. These descending neural networks are important, because they provide the mechanisms by which cognition, emotion, and attention act to modify the pain experience, particularly at the level of the spinal cord. Previous studies have shown that persistent pain associated with tissue and nerve injury results in increases in descending brainstem modulation. This is a bimodal effect; that is, descending inhibitory effects and descending facilitatory effects modulate the output of the spinal cord.

Neural glial interactions

It is known that glia play an active role in regulation of synaptic transmission in the CNS. Recent evidence has demonstrated the existence of dynamic and bidirectional communication between glia and neurons. Studies have shown that after injury, neuronal and glial interactions lead to neuronal hyperexcitability in descending circuits and increases in descending modulation.³ Glial cells are well-endowed with glutamatergic processes, which support the potential involvement of NMDA further in pain regulation.

Factors Affecting the Processing and Expression of Pain

M. Catherine Bushnell, PhD, Professor of Dentistry and Neurology at McGill University, addressed a body of research examining factors that influence and alter perception of pain, and to which she and her colleagues have made insightful and important contributions. Factors, such as attention, emotion, expectation, the placebo effect, and traumatic stress, as well as genetics, all play roles in determining the extent and magnitude of how pain is experienced, and also which areas of the brain respond to these stimuli.

Sensory and affective imaging studies have shown that even a brief experience of pain can activate widespread areas on both sides of the brain. In the descending modulation of pain, imaging studies have shown, information from the cortex can alter afferent input from the spinal cord.

Attention and mood modulate pain

People's experiences of pain can be greatly influenced by their attention to pain (focusing on it or ignoring it) and by mood (happy or depressed). The most startling examples are in traumatic stress, when pain can appear to be completely blocked. A classic example is the lessened impact of gunshot

injury on the battlefield. Imaging studies have revealed possible neural bases for this effect. Specific brain areas are activated when one engages in activities involving focused attention or when emotional reactions are evoked. Likewise, specific brain areas are activated during different types of pain states. Bushnell and other researchers are beginning to unravel how these two types of brain activity are mediated by separate neuromodulatory circuits. A promising strategy could involve changing the emotional and attentional modulation of pain as an intervention. For example, Bushnell and a colleague⁴ have showed that, while one can experimentally modulate mood or shift attention from pain, the perceptual consequences of these two interventions are different. For example, mood primarily alters pain unpleasantness, and attention preferentially alters pain intensity. These findings suggest that brain circuits involved in pain modulation provoked by mood or attention are partially separable. Likewise, the level and type of arousal are also important, and experimentally these effects can be separated and differentiated in the brain. The intrinsic modulatory brain systems that become activated with these psychologic factors are closely related to those stimulated when opiates are given for pain relief. This may indicate that psychologic factors could be used to complement conventional treatments for pain. Other psychologic factors, such as the level of anxiety one experiences or the anticipation of pain, can also affect the pain experience profoundly. Pain anticipation and the apprehension of a dire threat increase both pain and anxiety, as in the example of a child who reacts with great distress to an approaching needle for an injection. Activation of the anterior insula has been suggested as a specific marker for this type of distress.

Placebo analgesia and the expectation of pain relief

Placebo responses typically occur when people receive an inactive intervention when they are expecting a treatment for pain. This placebo response can actually have an analgesic effect. However, placebo analgesia is not just expectation. There is also a conditioning component, and studies have confirmed that this component also produces pain relief. In an initial series of studies, Benedetti and colleagues have shown that these effects can be studied separately and combined to produce even larger placebo effects. More recently, investigators have attempted to use similar designs to understand the underlying neurochemistry of the placebo response. In brain-imaging studies, placebo reduces pain-evoked activity in the anterior cingulate cortex (ACC), the insula, and the thalamus. The placebo increases prefrontal and midbrain activity in anticipation of pain relief and activates descending systems similar to those activated by emotional modulation. The ability to identify separate brain mechanisms associated with conditioning and expectation, and understand how they interact with various treatments to reduce pain will undoubtedly increase understanding of both pain mechanisms and treatments to reduce pain. Similar studies have addressed changes in the efficacy of acupuncture caused by psychologic factors.

Various neurotransmitters have been implicated in neuronal activity associated with pain, its treatment, and placebo analgesia. Positron emission tomography (PET), in which radioactive ligands bind to specific receptors in the brain, has allowed characterization of these receptors. μ -Opioid (one of

the three subtypes of receptors that opiate drugs bind to) and dopamine D2/D3 receptors are components of the neural pain pathways. Placebo activates μ -opioid receptors, and various studies have shown reduced binding potential for exogenous opiate when a patient experiences a placebo effect. For example, Amanzio and Benedetti⁵ found that different types of placebo analgesic responses were evoked by means of cognitive expectation cues, drug conditioning, or a combination of both.

The neuropeptide cholecystokinin exhibits antiopioid activity, and the blockade of cholecystokinin receptors can potentiate the placebo analgesic response.⁵ Serotonin and adenosine have been implicated in the actions of acupuncture analgesia, suggesting they also may play a role in pain, the placebo response, and psychologic modulation of pain responses. Because this field of research is relatively young, it is likely that a number of other neurotransmitter systems that have not yet been identified may be involved. Use of imaging modalities such as PET and functional magnetic resonance imaging (fMRI) will increase our understanding of pain-modulatory processes and pain-treatment.

Traumatic stress and pain

Investigators have gained additional insight into the mechanisms of pain modulation from research with patients who have chronic pain and in individuals who are exposed to extreme stressors. For example, pain, when it is chronic, can result in hyperalgesia or an increased sensitivity to pain. In some forms of persistent pain conditions such as fibromyalgia, patients also present with increased sensitivity to experimentally induced pain. While acute stress can produce a diminished pain response, like the unaware gunshot wound victim, chronic anxiety or stress can increase the experience of pain, causing hyperalgesia. In the military, there are numerous scenarios in which one might think that extremely stressful events, such as those producing post-traumatic stress disorder (PTSD), would have a profound impact on pain. Recent studies suggest a more-complex picture of the pain/anxiety experience in such individuals. Although PTSD is associated with chronic pain, a growing body of research suggests that patients with PTSD have reduced experimental pain sensitivity.⁶ It is as if these patients remain in a state of high acute stress although circumstances no longer justify it. Brain-imaging studies have shown a decrease in amygdala activation but an increase in insula activity. Treatments that make a positive impact on returning soldiers with PTSD will greatly facilitate understanding of the underlying differences in this disorder, and other pain disorders, such as chronic low-back pain.

Genetics and pain

A link between genetics and pain has been established, and ongoing research has identified a number of genes that influence pain in ways, such as congenital insensitivity to pain. The interactions of genetic, epigenetic, and other contributors and influences are complex. One finding is that redheads (mice and humans) are less pain-sensitive than others, because of genetic alterations that produce a non-functional melanocortin-1 receptor.⁷

Mechanisms of Acupuncture Modulation for Acute Pain (Laboratory Research)

Andrew C. Ahn, MD, MPH, Instructor of Radiology at Harvard Medical School and Assistant Professor of Neurosciences at Massachusetts General Hospital, led this session with a presentation that focused on the mechanisms by which acupuncture produces analgesia. Key findings have come from studies of the endogenous opioid system, CNS imaging, and the autonomic nervous system.

Acupuncture analgesia has been demonstrated for experimental pain using mouse, rat, and rabbit models⁸ and humans.⁹ On average, significant reduction in experimental pain was typically in the range of 20–40%. Analgesia was reduced or completely blocked by administration of the opioid antagonist naloxone. (Hence, these early studies postulated that acupuncture analgesia was, in part, mediated by an endogenous opioid system, in which enkephalin, β -endorphin, dynorphin, and endomorphin are secreted in the CNS and subsequently bind with μ -, δ -, or κ -opioid receptors. However, some later studies were unable to replicate acupuncture analgesia blockade by naloxone in humans,¹⁰ and more recently,¹¹ were unable to replicate naloxone blocking in a rat model of acute clinical pain (experimentally induced sprained ankle) but did demonstrate that acupuncture analgesia in this model came from spinal adrenoceptors as part of the descending inhibitory system. It was postulated that the effects of naloxone may have been more related to the stress induced by the experiment than the acupuncture, and cautioned that both animal models and human studies of experimental pain do not necessarily reproduce acute or chronic clinical pain conditions.¹⁰

The mechanisms of acupuncture analgesia in the periphery appear to be mediated by afferent nerves, and, when these nerves are either ligated or reversibly chemically deactivated, no subsequent analgesia is produced by acupuncture. Analgesia has been demonstrated for both manual acupuncture (i.e., insertion and twirling of a needle for ~2 minutes) and electroacupuncture (EA), with stimulation parameters typically of 1–4 Hz, 3–12 V, and 1–3 mA, with a pulse width of ~0.1 ms for ~20 minutes. In some cases, manual acupuncture and EA are combined, with the clinician first performing manual acupuncture to obtain the *de qi* sensation (commonly experienced as a dull aching pain) followed by EA. For EA, there appear to be dose–response effects, with stronger electrical stimulation (e.g., higher amperage) associated with greater analgesia. Both manual acupuncture and EA appear to be mediated by A- δ and C fibers, which synapse in lamina I and II of the dorsal horns in the spinal cord.

Imaging of the brain (mostly fMRI, but also magnetoencephalography [MEG] and PET) during acupuncture has demonstrated that many areas are stimulated, including the somatosensory cortex I and II, prefrontal cortex, insula, anterior cingulate cortex, thalamus, amygdala, hippocampus, hypothalamus, periaqueductal gray, reticular formation, and vermis of the cerebellum. When *de qi* is produced, there is a reduction in the BOLD signal (fMRI). EA appears to produce stronger activation of the brain than does manual acupuncture. The limitations of these imaging studies include the fact that most studies assess experimental rather than clinical pain, and the duration of the brain changes are unknown.

Moreover, placebo responses are confounding factors in acupuncture research that can be modulated. There appears to be a strong interaction between expectancy and acupuncture analgesia. In subjects receiving verum acupuncture, positive expectations amplified acupuncture analgesia (by sensory ratings and fMRI). In subjects with high expectancy (for benefit of acupuncture), clinical ratings of pain relief were similar for sham and verum acupuncture; however, fMRI changes were greater in verum than in sham acupuncture.

There are also studies examining the effects of acupuncture on the autonomic nervous system. Using a rat model of gastric distention-induced sympathetico-excitatory cardiovascular response, the Longhurst group¹² measured the change in mean arterial pressure (MAP) to manual acupuncture and EA (at 2, 10, and 40 Hz) at different point locations (PC 5–6, H 6–7, St 36–37, LI 6–7). In separate experiments using single unit recordings, the researchers also examined what types of afferents responded to the acupuncture and reported that the great majority of responses were by A- δ and C fibers for both manual acupuncture and EA, and that these afferents were much more responsive to lower frequency EA (i.e., 2 Hz) than higher frequency EA (i.e., 10 and 40 Hz). MAP was reduced by approximately 30% for all of the points stimulated except for LI 6–7, which showed no significant change. The observed effects lasted for tens of minutes, but faded within a few hours.

Summary

In summary, these studies, mostly using animal models have demonstrated that there are neurobiologically mediated effects of both manual acupuncture and EA. These effects require stimulation of peripheral afferents, which appear to be dominated by responses of A- δ and C fibers rather than A- β afferents. Subsequent to peripheral afferent stimulation, CNS centers respond with activation of the endogenous opioid system and/or descending inhibitory system to affect analgesia. Whereas peripheral afferent stimulation is immediate, CNS-mediated analgesia typically takes tens of minutes to reach maximum analgesia and lasts longer than the needling itself. Most studies have utilized experimentally induced acute pain rather than clinical pain, and there have been few studies of chronic pain.

Mechanisms of Acupuncture Modulation in Acute Pain (Human Research)

Brian Berman, MD, Director of the Center for Integrative Medicine at the University of Maryland, reviewed the cumulative evidence from systematic reviews and randomized controlled studies on the efficacy of acupuncture as an adjunct analgesic for acute pain. Since 1996, Berman has coordinated the Complementary and Alternative Medicine section of the Cochrane Collaboration, the “gold standard” for systematic reviews of primary research in human health care and health policy.

Published systematic reviews of acupuncture for acute pain conditions have focused primarily on postoperative pain and labor pain. The results of a review on postoperative pain showed that ~ 80% of patients experience pain after surgery, and opioids are most commonly used to treat the pain.¹³ However, this study also reported that the opioid-

related side effects of nausea, vomiting, pruritus, sedation, and dizziness could lead to a delay in recovery. The investigators concluded that adjuvant treatments are needed for postoperative pain control.

A search of Cochrane reviews of the use of acupuncture for acute pain produced 27 randomized controlled trials (RCTs) that evaluated whether adding acupuncture as an adjuvant to opioids for postoperative pain can reduce pain intensity and postoperative opioid consumption. The types of acupuncture interventions included in this group of trials were acupuncture, acupressure, acupuncture with moxibustion, and transcutaneous electrical nerve stimulation (TENS) at various acupoints. Only studies in which sham or placebo acupuncture was used as a control intervention were included. Relevant outcomes were postoperative pain intensity, postoperative opioid consumption, and opioid-related side-effects.

Fifteen RCTs met the Cochrane eligibility criteria, including different types of surgery (e.g., abdominal, maxillofacial, and knee surgery, and hip arthroplasty), different anesthesia conditions, and several types of acupuncture intervention and timing of acupuncture (before surgery, after surgery, and both). Berman reported that overall, analgesic consumption was significantly lower in the acupuncture group, compared to the sham/placebo group at 8, 24, and 72-hours. The morphine-sparing effect was 21% at 8 hours, 23% at 24 hours, and 29%—the largest effect—at 72 hours. The review's results are limited, however, by the wide variability in acupuncture regimens, types of surgery, time of application, durations of stimulation, and the inconsistent and often unsatisfactory reporting of outcome measures.

Berman emphasized the need for future RCTs to address the potential difference in efficacy between preoperative and postoperative acupuncture. He emphasized that such studies would increase our understanding of the mechanisms of pain relief through acupuncture; compare the potential analgesic effect of different acupuncture points and different techniques of acupoint stimulation; and evaluate acupuncture techniques as an integral part of multimodal analgesia regimens.

Berman then described his experience at the Center with the design and conduct of a randomized trial of acupuncture for acute dental pain and postoperative oral surgical pain. The study included three arms ($N=180$): real acupuncture, a sham insertion acupuncture control, and sham noninsertion (placebo) acupuncture. The sham acupuncture procedure was similar to verum acupuncture, with a needle noninsertion sham (needles taped on acupoints); needle-insertion sham (needles inserted at nearby sites with no manipulation); and mock electrical stimulation (ES). Healthy patients underwent a standard oral surgical procedure with local anesthesia and received acupuncture immediately after surgery. The patients were asked to rate their pain level on a visual analogue Scale (VAS) and on the Cooper-Beaver Four-Point Pain Scale. The measurements were repeated at 15-minute intervals until a level of pain occurred, or up to 6 hours. Other outcome assessments included survival time before the first report of moderate pain, and survival time before request for rescue medication.

A Kaplan-Meier curve comparison between verum acupuncture and placebo demonstrated that verum acupuncture performed better than placebo in median duration, suggesting that acupuncture increased postoperative pain-free

time and significantly lengthened the time to rescue drug, compared to placebo.

Patients in the verum acupuncture treatment group had a significantly longer median survival time-to-rescue drug compared to placebo. The verum acupuncture group had more pain-free time before their first pain versus placebo.¹⁴

Through the efforts of Berman and colleagues, acupuncture is being integrated into shock trauma services at the University of Maryland Medical Center. Over the past 3 years, acupuncture treatments were provided to more than 300 inpatients who had shock trauma. An ongoing pilot study is evaluating whether acupuncture can reduce mild traumatic brain injury (mTBI) following injury and/or reduce specific affective and somatic symptoms such as pain.

To apply these data to battlefield and emergency-care settings, issues of context and timing are extremely important. Context and expectation have been demonstrated to influence pain perception and response to treatment. Factors, such as types of pain, phases of acupuncture analgesia, time and duration of exposure to acupuncture, and subject sensitivity to opioid drugs are critical in the battlefield and trauma settings. These factors need to be incorporated into studies assessing acupuncture as adjunct therapy for acute pain. Another gap that needs to be addressed is systematic genotype/phenotype characterization of subjects recruited in trials of acupuncture for acute pain.

Overview of Clinical Studies of Acupuncture and Pain

Andrew Vickers, PhD, Associate Attending Research Methodologist, Memorial Sloan-Kettering Cancer Center, and Chair of the Acupuncture Trialists' Collaboration, provided an overview of clinical studies on acupuncture and pain. He described the Acupuncture Trialists' Collaboration¹⁵ and presented conclusions regarding the efficacy of acupuncture for chronic pain conditions. To answer the question of whether acupuncture can help ease trauma pain, Vickers described examples of research data from clinical trials on trauma pain and other trauma symptoms. He provided recommendations for future research on acupuncture and trauma/acute pain in the military and other settings.

A large number of individual trials of acupuncture for low-back pain and a number of systematic reviews have been published: 17 Cochrane Collaborative reviews of acupuncture for pain and an additional 26 non-Cochrane systematic reviews. However, the difficulty with existing systematic reviews, and the rationale for the Acupuncture Trialists' Collaboration, is that in systematic reviews, the sample size of the included studies is often too small. In addition, the methodological quality of the studies is questionable, and the conclusions the reviewer can draw from the data are thus very tentative.

To address these shortcomings, the Acupuncture Trialists' Collaboration uses only raw data from the highest quality randomized trials and a combined individual patient data set. Individual patient data meta-analysis allows trials with different analytic methods to be combined (e.g., measures of mean pain versus 50% reduction in pain). This type of meta-analysis increases statistical power with analysis of covariance (ANCOVA) versus unadjusted analyses, improves data quality, and facilitates meta-regression, such as to answer the question of whether baseline pain severity affects outcome.

The Acupuncture Trialists' Collaboration included trials of acupuncture for one of four chronic pain conditions. Pain must have been measured more than 4 weeks after the first acupuncture session, and allocation concealment must have been unambiguously determined to have been adequate.

Examples of allocation strategies that are unconcealed, Vickers said, are lists of names, on which selection bias can occur, and envelopes that can be opened. Envelope randomization was acceptable only when specific procedures were in place to ensure allocation concealment. Only trials that were absolutely ensured to have allocation concealment were included in the Collaboration.

The primary endpoint of the meta-analysis determined the effect size of acupuncture. Secondary endpoint analyses included medication use, physical well-being, mental well-being, and overall quality of life. The use of individual patient data meta-analysis method also allowed assessment of the effect of acupuncture by indication or by acupuncture characteristics, such as duration or frequency of sessions, time course of effects and effects of different types of shams.

The first phase of the Acupuncture Trialists' Collaboration, consisting of a systematic review to identify eligible studies, has been completed through November 30, 2008. Thirty trials, with more than 18,000 patients, were included. All trials were evaluated for methodology by three independent evaluators for inclusion criteria and blinding. The second phase involved collation and checking of raw data. Raw data were obtained from 29 of 31 studies, and no major discrepancies were discovered after checking data. The third phase, the meta-analysis, has been completed, with results submitted for publication.

In an informal review, Vickers described findings from several acupuncture trials on trauma pain. One study¹⁶ involved 100 military personnel who presented to an emergency department with acute pain. Patients received either semipermanent auricular acupuncture needles or no needles (control). The pain score was determined on a 0–10 VAS. Results were a 2.3 reduction in pain in the treatment group and a 0.2 pain reduction in the control group, a significant difference between groups ($p < 0.001$).

Another study involved 11 patients with burns in a crossover design. Patients were randomized to TENS stimulation or a placebo pill. Pain was evaluated by a 0–10 VAS. Results were an average VAS score of 2.5 in the treatment group and 4.3 in the control group, a significant difference between groups ($p < 0.002$).¹⁷ Barker et al.¹⁸ published results from 38 patients with hip fracture who received either auricular or sham acupressure administered by an ambulance paramedic. Pain was assessed on a 100-mm VAS. Pain scores were 35 mm in the verum acupressure group versus 70 mm in controls, for a significant difference between groups, $p < 0.01$.

Trials on pain and other trauma symptoms, based on informal reviews, have shown less pain and anxiety in an acupressure group^{19–21} and less nausea in an acupressure group.²² Vickers outlined “three golden rules” for research, based on standards that were adopted by the Acupuncture Trialists' Collaboration and his own recommendations:

- (1) *High quality trials*—Use only trials with appropriate allocation concealment, ensure data quality, and use ANCOVA for reporting of intergroup differences.

- (2) *Power*—Very large sample sizes are needed. In a typical trial of acupuncture versus sham, the effect size is 1/5 or 1/6 of a standard deviation. This leads to sample sizes of 750–1500.
- (3) *Data*—Keep well-annotated data sets suitable for sharing with a third party.

In conclusion, Vickers noted that researchers who conduct studies on trauma pain (typically with small numbers of patients) should learn from the experience of chronic pain researchers. Large sample sizes are needed to conduct the examples of effectiveness studies suggested by the Placebo Controlled Studies Breakout Group. During the meeting proceedings, a suggestion was made to set up official liaisons from components of DoD and NIH with a goal of having an official advisory group. This group could ensure that these recommendations or principles for high-quality study design are followed to move research forward on acupuncture for treating acute pain in the military.

Use of Placebo in Acupuncture Pain Studies

In a review of placebo options in acupuncture pain studies, Karen Sherman, PhD, MPH, Senior Investigator from the Group Health Research Institute, addressed five topics: (1) sham controls for acupuncture; (2) taxonomy of sham controls for acupuncture studies; (3) if the type of sham control matters; (4) dilemmas from pain trials in the United States and Europe; and (5) translation of studies into helpful concepts for managing acute pain on the battlefield.

In efficacy studies of acupuncture, sham treatments fall into three broad types: nonidentical shams; insertive sham needling, and noninsertive sham needling. The challenges of using nonidentical sham treatments (e.g., laser acupuncture or sham TENS treatment) are that, by definition, they do not resemble the active treatment and they require deception, which can lead to difficulty in interpreting the results. Sham needling has many variations; yet, each variation leads to a slightly different research question being assessed (importance of specific locations, depth of needling, and stimulation of the acupuncture needle). The final option for control conditions in acupuncture studies is noninsertive needling, including “stage daggers,” which give the appearance of skin penetration but use a blunt-tipped needle that does not actually pierce the skin.

Several conceptual and implementation challenges are associated with the use of most sham acupuncture options. Acupuncture naïve patients may be required to ensure credibility of the sham. Shams may compromise needle manipulation in the verum group because of interference from the device needed to mask verum and sham treatments. Some of the sham options can be challenging to use in difficult anatomical locations (e.g., the scalp). Most importantly, it is not clear whether all sham treatments are truly inert.

Sherman provided an overview of the literature on various sham acupuncture options. Occasionally, more than one sham condition was used in a single study, allowing direct comparison. This has been done in studies of fibromyalgia, carpal tunnel syndrome, and low-back pain. Results indicate that using insertive sham conditions that vary only needle location (off point) and stimulation of the needle (*de qi* sensation) does not result in a separation from verum acupuncture in these pain conditions. Dincer and Linde,²³

reviewed sham acupuncture use in clinical studies. These researchers reported that there were no overall differences in the results by type of sham used, and that the outcomes achieved from each type of sham acupuncture were quite heterogeneous. Sherman emphasized that there is a need for better understanding of how these sham treatments work and suggested that, for pain conditions, noninsertive or nonidentical sham controls be used.

Sherman highlighted the dilemmas of interpretation for many large clinical trials of acupuncture: most studies have demonstrated that patients receiving verum acupuncture, noninsertive sham acupuncture, and insertive sham acupuncture generally have better outcomes than those receiving usual care or members of wait-list control groups. However, the separation of verum acupuncture from insertive or noninsertive sham acupuncture is usually not demonstrated (notable exceptions include verum acupuncture for osteoarthritis (OA) of the knee in the German Acupuncture Randomized Trial (ART) and modest efficacy for verum acupuncture for low-back pain. Whether noninsertive acupuncture is a viable treatment or a strong placebo is an important question for interpretation of the findings.

Overall, the clinical studies of acupuncture suggest that acupoint specificity does not seem to be important and that insertive stimulation may not be necessary. In a larger context, Sherman suggested that the acupuncture field still does not know how acupuncture works; making the creation of a sham intervention that removes the active component difficult.

In thinking about translating acupuncture research to battlefield situations, it is important to note that soldiers probably do not care how pain relief is achieved. Placebo effects on the battlefield may differ from those in typical clinical settings as a result of patient–medic interactions, and the use of acupuncture shams or placebos is likely to be inappropriate in battlefield settings, so pragmatic trials should be considered.

Ted J. Kaptchuk, PhD Associate Professor of Medicine, Harvard University, introduced the concept of “malleability” of placebo effects and their dependence on behaviors embedded in medical rituals. Kaptchuk and colleagues²⁴ conducted a 2-week randomized controlled trial of sham acupuncture and a placebo pill, in patients with persistent arm pain. The researchers used the Pransky’s upper extremity-function scale, and grip strength to assess the severity of symptoms. After 2 weeks of the placebo run-in period, there was no difference in pain severity between study groups, but function improved, especially the ability to sleep, more in the placebo-pill group. In the continuation study of 6 additional weeks, the sham needle was superior to the placebo pill for pain relief. Kaptchuk proposed that the placebo effect of a clinical encounter can be divided into three main components: assessment/observation; therapeutic ritual (as placebo); and the patient–provider relationship.

In a 6-week randomized controlled trial, Kaptchuk and his colleagues investigated whether the three components of the clinical encounter could be separated and then progressively combined to produce incremental improvements in patients with irritable bowel syndrome.²⁵ Subjects were randomized to: a wait-list control group who received usual care from a gastroenterologist; placebo acupuncture with limited interaction with a practitioner; or placebo acupuncture with an

augmented patient–practitioner relationship. Components of the placebo effect that contributed to the placebo effect were able to be combined progressively in a manner analogous to a “graded dose escalation” in medical therapy, with the patient–practitioner relationship emerging as the most important and impactful component.

Kaptchuk discussed a Cochrane review on placebo interventions for all types of conditions that suggested that sham acupuncture interventions might be associated with larger effects than pharmacologic and other physical placebos. In the case of acupuncture for chronic low-back pain, Kaptchuk concluded that evidence suggests that acupuncture, currently, is barely better than placebo controls but significantly better than usual care. He asked if the question for the military was (1) if acupuncture benefits patients or (2) if acupuncture is better than placebo. Each of these questions could have distinct answers.

Comparative Effectiveness Research in Acupuncture for Acute Pain

Wayne Jonas, MD, President and Chief Executive Officer of the Samueli Institute and Associate Professor at the Uniformed Services University of the Health Sciences, Bethesda, Maryland, presented data indicating that 25% of military personnel with pain have narcotics addiction. He highlighted the need for alternative treatments to opioids for management of pain from war-related injuries; acupuncture may be one of those alternatives. Jonas referred back to the 1997 NIH Consensus Conference that determined that there was sufficient evidence to conclude that acupuncture is safe and effective for postoperative pain and postoperative nausea and vomiting. Yet, he noted that, today, acupuncture is rarely used in postoperative settings and that the evidence is not translating into practice.

According to the standard research evidence hierarchy, reviews and meta-analyses are the most important types of evidence, followed by case series, case reports, qualitative research, and anecdotes. Jonas argued that this framework favors certain audiences and potentially creates a number of problems for the ethical delivery of patient-centered care. Jonas showed an example of how the differential importance of meaning and context affects the choice between treatment A (acupuncture) and treatment B (nonsteroidal anti-inflammatory drugs; NSAIDs).²⁶ The evidence hierarchy favors the NSAIDs, whereas the patient-centered approach favors acupuncture.

Decision points in medicine involve several stakeholders. These include the patient, the practitioner, the scientist, and the payor.²⁷ Each of these stakeholders values a different type of evidence. Payors value evidence at the top of the hierarchy—reviews and meta-analyses—in which a treatment or drug has been shown to work repeatedly in large groups. Basic scientists want to see laboratory evidence. Practitioners want observational research in real practice. And patients often are convinced by case reports and stories captured by qualitative research. By working from the evidence hierarchy (i.e., with reviews and meta-analyses at the top), interests of other viewpoints are minimized. One alternative is to align the audience with research methods and research goals. The Evidence House, which divides the question of evidence into rigor and relevance types, allows

quality evidence to be produced that aligns with the priorities of multiple stakeholders.²⁸

Jonas suggested that research on complementary therapies needs to be approached using other models, such as the Evidence House; the circular model, which takes an iterative approach to effectiveness and efficacy; or the “reverse phases” model, which takes into account that the majority of CAM information comes from clinical practice. The Society for Acupuncture Research uses an approach that places the patient in the middle of a bidirectional line with the bench (laboratory research) on one side and the community on the other. The emphasis in this model is ecologic validity.

There are a number of scales and checklists to assess the validity of RCTs including one from Cochrane (www.cochrane.org), for which validity criteria include sequence generation, allocation, blinding, incomplete outcome data, and selective outcome reporting. The STRICTA [Standards for Reporting Interventions in Controlled Trials of Acupuncture] 2010 Checklist may be used for reporting interventions in a clinical trial of acupuncture (STRICTA 2010 Criteria; <http://www.stricta.info/>). Observational studies (e.g., quality of life [QoL] post acupuncture treatment) draw inferences about the possible effect of a treatment on subjects, in which the assignment of subjects into a treated group versus a control group is outside the control of the investigator. Qualitative research captures the patient’s perspective.

Comparative effectiveness research (CER) is relevant to the study of acupuncture. The definition of CER includes the following key elements of (1) direct comparisons of effective interventions, (2) study of patients in day-to-day clinical care, and (3) tailoring decisions to individuals patients’ needs.

Acupuncture randomized trials, such as the German Randomized Acupuncture (GERAC) trials in low-back pain²⁹ OA,³⁰ and chronic shoulder pain,³¹ are examples of CER that have generated thought-provoking results that defy easy explanation. Most (but not all) studies show that sham and verum acupuncture performed better than standard care but were almost equivalent to each other.

Jonas also discussed AIM (Acupuncture in the Military) research collaboration organized by the Samueli Institute examining research, practice, and policy goals for acupuncture in the military. AIM initiatives include U.S. Air Force projects involving patients with acute pain, an observational study of clinical outcomes related to pain, and a feasibility study that integrates ear acupuncture into the aeromedical evacuation system. Ear or “battlefield” acupuncture (BA) has been studied for the treatment of acute pain. Goertz and colleagues¹⁶ published evidence showing significant improvement in pain in patients within 1 hour in the emergency department. The impact of acupuncture for longer periods of time has been examined in a study of acupuncture for chronic pain in a military medical center³²; 65% of patients who received acupuncture were significantly improved after 4 weeks. Currently, Jonas, French, Wallerstedt, and colleagues are undertaking a CER study using a three-armed randomized design to compare two acupuncture methods and standard care for treating headaches associated with traumatic brain injury.

Other current CER acupuncture studies in the DoD/Veterans Affairs (VA) involving military personnel include: (1) acupuncture for the treatment of post-traumatic stress at Walter Reed Medical Center; (2) auricular acupuncture for

acute pain in transport of wounded personnel; and (3) acupuncture for pain and QoL in veterans with PTSD. Among 100 priority topics for CER, the Institute of Medicine (IOM) lists as number 56: “Compare the effectiveness of acupuncture for various indications using a cluster RCT.” The potential of leading a national effort to produce practical evidence for using acupuncture to treat pain could be realized by a partnership between the NIH and DoD in sponsoring a cluster RCT with the NIH providing scientific leadership and the DoD providing study sites.

Real-World Experiences

Richard Niemtzow, MD, PhD, MPH, Colonel (Ret), USAF, a radiation oncologist, shared his experience as the first full-time acupuncturist in a radiation oncology department. This acupuncture clinic became so popular that, in 2002, Niemtzow started the first full-time acupuncture clinic for the U.S. Air Force at Andrews Air Force Base (now Joint Base Andrews).

Niemtzow described an early demonstration of successful use of auricular acupuncture, his role in its subsequent adoption in the Armed Forces for use in battlefield situations, and recent studies that are contributing to an evidence base for BA use in emergency and clinic settings. Auricular acupuncture in particular is easy to use and easy to teach, and it has not been associated with side-effects or infection.

The efficacy of BA and clinical use of acupuncture in the military have been substantiated by brain-imaging studies and clinical studies. In the first randomized controlled trial in the Air Force, Goertz, Niemtzow, and colleagues¹⁶ compared standard emergency medical care to auricular acupuncture plus standard emergency medical care in patients with acute pain. Patients in the acupuncture group experienced a significant 23% reduction in pain. Acupuncture is also a useful tool for health care in an operational medicine environment.³³ Cost comparisons were also reported in this trial. The weekly cost of acupuncture needles was \$1.82 versus \$10.08 for weekly ibuprofen and \$20.58 for weekly celecoxib.

In an observational study conducted at an acupuncture clinic at Joint Base Andrews, patients with either acute and chronic pain, who had not responded adequately to Western medicine, and who were treated with several acupuncture modalities, experienced highly significant improvements in both mental ($p < 0.01$) and physical ($p < 0.001$) parameters at 4 weeks after the first acupuncture treatment.³⁴

Niemtzow emphasized that multiple treatments can be effective for reducing pain, and that pain relief is not always temporary, but “can last up to years.” A database from the U.S. Air Force acupuncture program at the Helms Medical Institute is a useful snapshot of the scope of acupuncture use (e.g., back and neck pain, headache, upper-extremity pain, complex pain, and psychiatric-related pain) and its benefit (average improvement scores: 17% are 90% better; 25% are 50% better; and 74% are 42% better. Acupuncture is an especially valuable option for pilots, who cannot take ibuprofen because of its tendency to cause blurred vision.

Niemtzow highlighted some initiatives that represent opportunities to acquire real-world data: “Acupuncturists without Borders,” an organization that responds to disaster settings in the United States and abroad, and the Pan-African Acupuncture Project. Also, from January through April of

2011, the U.S. Air Force conducted a feasibility study into integrating ear acupuncture for pain in patients being transported by the aeromedical evacuation system.

The military is faced with the daunting problem that large numbers of soldiers leave the battlefield with mTBIs and are heavily sedated for transport to military hospitals. Niemtzow opined that BA could provide an alternative strategy for patients who do not respond to Western medicine.

Robert Bonakdar, MD, Director of Pain Management at the Scripps Center for Integrative Medicine, reviewed evidence for the potential mechanisms of auricular acupuncture and future directions in its use. Auricular therapy involves the stimulation of the ear by various transcutaneous and percutaneous methods for therapeutic benefits. These methods may include pressure, electrical, light, and needle-based stimulation used alone or in combination. The therapeutic effects of auricular therapy are supported by a strong scientific foundation. In animal and human models, auricular therapy, particularly electrical percutaneous stimulation, has been shown to positively modulate vagal tone. fMRI examination of the somatosensory effect of auricular therapy has shown the potential existence of the somatotopic map.

Descriptions and references to auricular therapy are found in both Eastern and Western medical systems, including Greek, Roman, Persian, and Egyptian, dating back to at least the fourth century BCE. In the 1950s, Nogier described the somatotopic map of the ear. Auricular therapy has demonstrated potential benefit in a number of settings: acute pain syndrome; acute burn pain; hip fracture; migraine; chronic low-back pain; surgical pain; procedure-related anxiety; and mood and depression, among others.

Current clinical applications and areas of interest utilize the VIPER [Verbal Description, Inspection, Palpation, Electro diagnostic, Rx, and reassess] protocol for auricular therapy, an acronym that summarizes steps for detection and stimulation of auricular points. Examples of use of the VIPER protocol for acute pain in the military include a tolerability assessment in Fallujah, Iraq and a randomized study of auricular therapy for treatment of acute musculoskeletal pain in 250 military personnel. Other initiatives include an investigation of changes in the autonomic nervous system, in particular heart rate variability, when auricular therapy is utilized for acute or chronic pain.

Overall, auricular therapy, which modulates the autonomic nervous system, possibly through vagal nerve stimulation, is a novel and well-tolerated means of addressing pain and pain-related conditions.

Remy Coeytaux, MD, PhD, an Associate Professor in Community and Family Medicine at Duke University, highlighted two real-world experiences for which results will probably provide valuable evidence for using acupuncture in military settings.

One experience involves using acupuncture during aeromedical evacuation. Results from this study, which includes no comparator and will collect self-reported pain measures, will not only determine whether the intervention is feasible in this setting, but also if it is well-received by patients as well as providers.

The other is a DoD study for using acupuncture to reduce narcotics use and dependence in patients with traumatic brain injuries, with a primary outcome of headache-related

QoL. These real-world experiments will provide a comparison of Eastern and Western medicine, and present an opportunity to answer a number of questions that will have important clinical implications overall, not only to the military.

Gaps and Opportunities in Acupuncture and Acute Pain Research

Capt Anita Hunt Hickey, MD, Medical Corps, United States Navy, summarized the results of the 1997 NIH Consensus Conference on Acupuncture and the 2007 Society for Acupuncture Research Symposium White Paper.^{35,36} The goal of the conference was to provide clinicians, patients, and the public with a responsible assessment of the effectiveness of acupuncture for a variety of conditions. The NIH Consensus Conference Panel identified a series of needs and issued the following recommendations to bridge the gaps in advancing acupuncture research:

- Uniformity in training, licensure and credentialing
- Processes for uniform consent, patient grievances, and professional censure
- Improved access to acupuncture and medical services, with communication between acupuncturists and physicians
- Removal of financial barriers and improving insurance coverage for acupuncture as a treatment
- Dissemination of information to improve informed decision making regarding appropriate use of acupuncture.

This panel also made recommendations regarding the design and conduct of high-quality RCTs. These trials should be designed with enough rigor to permit clear evaluation of the effectiveness of acupuncture and should place an emphasis on acupuncture as it is used in clinical practice. Epidemiologic and outcomes research was also identified as a gap area.

In 2007, the Society for Acupuncture Research (SAR) sponsored a symposium and subsequently published a White Paper that revealed “considerable maturation” in acupuncture research since the 1997 Consensus Conference. However, acupuncture research is still faced with two major paradoxes.

First, although there is mounting evidence from large-scale effectiveness trials that acupuncture treatments are superior to usual care for some chronic conditions, verum acupuncture treatments are, at most, only marginally more effective than sham acupuncture. This finding is apparently at odds with traditional theories regarding acupuncture point specificity. Moreover, sham acupuncture, compared to no treatment, is associated with larger effect sizes than when conventional placebos are compared to no treatment. There is no conclusive evidence indicating which individual components of acupuncture are directly associated with therapeutic benefit.

The second paradox highlighted the difference between laboratory studies and results from clinical trials. Although studies in experimental animal models reported physiologic effects that varied as a result of needling parameters (e.g., needle-insertion depth, needle type, mode of stimulation, frequency of needle stimulation), the extent to which these

parameters influenced therapeutic outcomes in clinical trials was unclear.

Acupuncture treatments are complex multicomponent interventions consisting not just of needling components, but also of nonneedling components including psychologic (history, diagnosis, education) and physical components (palpation, moxibustion), as well as nonspecific components, such as time, attention, credibility, and expectations. A component of the interaction between practitioner and patient is the practitioner's intention for a therapeutic outcome, which is traditionally described as *yi*.

Acupuncture treatments should be studied as multicomponent, whole-system interventions using a practical systems perspective (top-down approach) and in mechanistic studies that focus on understanding individual treatment components and how the effects of these components interact and translate into clinical outcomes (bottom-up approach).

Breakout Sessions Summary

Daniel C. Cherkin, PhD, a Senior Scientific Investigator with the Group Health Research Institute moderated a panel discussion with breakout group leaders and participants in the workshop. Four main questions were addressed: (1) the greatest unmet needs of military/emergency care patients who have acute pain and the highest priorities for research; (2) the most promising opportunities for using acupuncture to address these needs; (3) existing adequate evidence for justifying acupuncture use in military/emergency care settings; 4) the next steps for developing basic and clinical studies in military populations.

All participants in the workshop recognized the urgent need to implement innovative and effective strategies for treating combat military personnel as well as veterans from Iraq and Afghanistan. There are a significant number of soldiers experiencing various complex problems that are not being addressed, including pain, anxiety, separation, and PTSD. The military is committed to exploring holistic approaches to meet the needs of patients with acute conditions. This change in perspective focuses on treatment for "a patient with pain" rather than just treating pain.

The potential to incorporate acupuncture as a component of standard care has been hampered by the lack of evidence-based studies in trauma and military settings. Three breakout groups at the workshop—the placebo-control, comparative effectiveness, and mechanistic-studies work groups—provided practical recommendations to allow for clear results that would be available in a short-term time frame.

Claudia Witt, MD, MBA, the Director of the Institute for Social Medicine, Epidemiology and Health Economics at the University Medical Center Charité in Berlin, led the placebo-control work group. A consensus was reached that there is not enough evidence for acupuncture treatment for acute pain. The group recognized that the specific effects of acupuncture for acute pain (verum acupuncture versus sham acupuncture) would be small, and to detect a significant difference, sham-controlled studies would require large samples to be powered sufficiently. Although sham-controlled trials would help identify relevant context effects and inform ongoing acupuncture practice in military settings, the

group agreed that it may be more practical to first conduct such trials in a civilian setting. Two possible trial designs were suggested:

- (1) A cluster randomized trial—this may be designed by "randomizing" medical evacuation planes on which the physician also provides acupuncture. Depending on which plane patients board as they are being evacuated from the battlefield, they may receive acupuncture in addition to usual care or usual care only. A possible endpoint could be the intake of opiate drugs.
- (2) A pragmatic RCT with patients who come back from the battlefield—this type of study could compare patients presenting with acute pain. In one group, patients would receive acupuncture in addition to usual care. In another group, patients would receive usual care only. The endpoints would be patient-centered outcomes and biomarkers. This trial could be also done as a cluster randomized trial (randomizing treatment centers and also including biomarker investigation).

The placebo-control workgroup also highlighted the need to conduct CER in military settings. CER studies could focus on effectiveness and include aspects of dosing and cost-effectiveness. Retrospective data, prospective observational data, or small dosing studies that reflect usual care in the military would be useful for assessing acupuncture intervention in CER.

Col Richard Petri, Director of the Department of Defense's first Center for Integrative Medicine at William Beaumont Army Medical Center (WBAMC), led the comparative effectiveness studies breakout group. The group recognized the importance of establishing baseline data on the effects of acupuncture on acute pain to ascertain the relevant questions in conducting CER. Specifically, the following parameters would need to be assessed in the context of military settings: (1) type of acute pain; (2) acute/chronic or acute pain, compared to chronic pain exacerbations; (3) population; (4) patients' profiles for successful acupuncture studies; (5) availability of acupuncturists; and 6) patients' individual data and patient-based outcomes. The group agreed that a full CER study is currently not feasible. This workgroup embraced a stepwise process, starting with pilot CER feasibility studies and more-rigorous larger studies followed by RCTs.

Implementation of acupuncture treatment programs poses several challenges in military settings. These include: (1) the feasibility of delivering the acupuncture treatment on the battlefield, compared to treatment in a military hospital; (2) access to follow-up treatment for soldiers who have returned to their bases; (3) an optimal acupuncture protocol for long-term treatment after the transition of acute to chronic pain; and (4) integration of acupuncture into standard military care practices, such as regional anesthesia and drug regimens.

Richard Hammerschlag, PhD, Emeritus Dean of Research, at Oregon College of Oriental Medicine, led the mechanistic-studies breakout group. This group highlighted several advantages to promoting basic science studies focused on the mechanism of acupuncture in general and on acupuncture analgesia in particular. A clearer understanding of how acupuncture modulates pain would strengthen acceptance of acupuncture as a safe and effective clinical modality, and

have a translational impact on clinical decision making regarding when acupuncture may be an effective alternative or adjunct treatment to pain medication. While elegant studies have revealed strong correlations between acupuncture needling and release of endogenous opioids, animal models are needed to help clarify the cellular and molecular bases of the body's initial responses to the acupuncture needle. The rationale for these types of studies is especially compelling in a military setting, because many troops facing active duty will be subjected to acute pain and many will progress to chronic pain.

The group reached consensus on several recommendations for physiologic and psychophysiologic studies. First, a package of baseline tests should be developed for use at major deployment centers, with the resulting data contributing to development of personalized medicine. Such tests can help provide answers to such key questions as: why some individuals are good responders and others poor responders to acupuncture analgesia; why acute pain in some individuals does/does not progress to chronic pain; and why some individuals do/do not experience phantom-limb pain. Five specific tests were recommended:

- (1) Identification of pain-related single nucleotide polymorphisms (e.g., those involving endogenous opioid receptors)
- (2) Sensory screening to establish experimental pain profiles
- (3) Assessment of psychologic profiles (e.g. catastrophizing)
- (4) Adaptation of existing test batteries to a military context (e.g., Orofacial Pain Prospective Evaluation and Risk Assessment [OPPERA] designed for prospective TMD/chronic pain study); Patient Reported Outcomes Measurement Information System [PROMIS])
- (5) Establishment of autonomic nervous system functions as measures of adaptability and resilience (e.g. heart rate variability).

The group's second recommendation was that the military consider designing and implementing studies that address the following questions:

- Do effects of trauma and acute battlefield stress modify effectiveness of acupuncture with/without opioids for acute pain?
- Can acupuncture reduce the use of opiates for treatment of acute pain and for which patients is this effective?
- Based on current knowledge of acupuncture mechanisms, what are the most feasible research studies that can be done in military settings?
- What would be the effects of nerve blocks, acupuncture, or both (asked to assess pain outcomes and trajectory of healing, because acupuncture is a holistic treatment and may stimulate bodywide self-regulatory, self-healing mechanisms)
- Is auricular acupuncture is effective instead of ketamine? (Navy SEALs are crosstrained as corpsmen (medics, e.g., to use IM ketamine [acts similar to a local anesthetic] as an adjunctive to opiates.)

Conclusions

Workshop participants gained a better appreciation of the urgent need to develop the evidence base to determine

whether it is appropriate to integrate acupuncture in standard care regimens in military settings. The DoD researchers challenged the group to identify the greatest unmet needs in the military both for the management of acute pain and development of research priorities with this compelling call: "Come and join us in the trenches and come and take us to your benches." Potential future steps are:

- Systematic collection of baseline data in military populations (genotype and phenotype, demographic, physiologic, behavioral data, etc.)
- Development of a comprehensive common data-elements package, including consent form, institutional review board requirements, and outcome measures with appropriate test batteries
- Further scientific exploration of holistic strategies to address acute pain while reducing the potential for addiction to opioid medications
- Integration of evidence-based complementary health strategies to address psychologic and mental health issues in military settings
- Design of studies of acupuncture as adjunctive treatment to usual care (e.g., acupuncture + anesthesia versus anesthesia)
- Focus on interactions of acupuncture effects with psychologic factors—assessment of cumulative time soldiers are kept out of the operating theater after acupuncture treatment for symptom management of pain and psychologic dysfunction
- Leveraging of existing infrastructure of ongoing initiatives in trauma-spectrum disorders (DoD Centers of Excellence); NIH and Veterans Administration-funded studies of PTSD comorbid with somatic problems and cognitive difficulties; and NIH assessment tools such as patient reported outcome measurement information system and OPPERA
- Utilization of cumulative data gathered on the effect of acupuncture for chronic pain
- Design prospective studies comparing acupuncture to neurosurgery or nonsurgical disc treatment for chronic back pain.

Disclosure Statement

The authors have no conflict/competing financial interests.

References

1. Dubner R, Ruda MA. Activity-dependent neuronal plasticity following tissue injury and inflammation. *Trends Neurosci* 1992;15:96–103.
2. Dubner R. The neurobiology of persistent pain and its clinical implications. *Suppl Clin Neurophysiol* 2004;57:3–7.
3. Ren K, Dubner R. Neuron-glia crosstalk gets serious: Role in pain hypersensitivity. *Curr Opin Anaesthesiol* 2008;21:570–579.
4. Villemure C, Bushnell MC. Mood influences supraspinal pain processing separately from attention. *J Neurosci* 2009;29:705–715.
5. Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. *J Neurosci* 1999;19:484–494.

6. Kraus A, Geuze E, Schmahl C, et al. Differentiation of pain ratings in combat-related posttraumatic stress disorder. *Pain* 2009;143:179–185.
7. Mogil J, Ritchie J, Smith S, et al. Melanocortin-1 receptor gene variants affect pain and μ -opioid analgesia in mice and humans. *J Med Genet* 2005;42:583–587.
8. Pomeranz B. Do endorphins mediate acupuncture analgesia? *Adv Biochem Psychopharmacol* 1978;18:351–359.
9. Ahn AC, Ngo-Metzger Q, Legedza AT, et al. Complementary and alternative medical therapy use among Chinese and Vietnamese Americans: Prevalence, associated factors, and effects of patient-clinician communication. *Am J Public Health*. 2006; 96(4):647–53.
10. Chapman CR, Benedetti C, Colpitts YH, Gerlach R. Naloxone fails to reverse pain thresholds elevated by acupuncture: Acupuncture analgesia reconsidered. *Pain* 1983;16:13–31.
11. Koo ST, Lim KS, Chung K, Ju H, Chung JM. Electroacupuncture-induced analgesia in a rat model of ankle sprain pain is mediated by spinal alpha-adrenoceptors. *Pain* 2008;135(1–2):11–19.
12. Zhou W, Fu LW, Tjen-A-Looi SC, Li P, Longhurst JC. Afferent mechanisms underlying stimulation modality-related modulation of acupuncture-related cardiovascular responses. *J Appl Physiol* 2005;98:872–880.
13. Sun Y, Gan TJ, Dubose JW, Habib AS. Acupuncture and related techniques for postoperative pain: A systematic review of randomized controlled trials. *Br J Anaesth* 2008;101:151–160.
14. Lao L, Huang Y, Feng C, Berman BM, Tan MT. Evaluating Traditional Chinese Medicine using modern clinical trial design and statistical methodology: Application to a randomized controlled acupuncture trial. *Stat Med* 2012;31:619–627.
15. Vickers AJ, Cronin AM, Maschino AC, et al; Acupuncture Trialists' Collaboration. Individual patient data meta-analysis of acupuncture for chronic pain: Protocol of the Acupuncture Trialists' Collaboration. *Trials* 2010;11:90.
16. Goertz CM, Niemtzow R, Burns SM, Fritts MJ, Crawford CC, Jonas WB. Auricular acupuncture in the treatment of acute pain syndromes: A pilot study. *Mil Med* 2006;171:1010–1014.
17. Lewis SM, Clelland JA, Knowles CJ, Jackson JR, Dimick AR. Effects of auricular acupuncture-like transcutaneous electric nerve stimulation on pain levels following wound care in patients with burns: A pilot study. *J Burn Care Rehabil* 1990;11:322–329.
18. Barker R, Kober A, Hoerauf K, Latzke D, Adel S, Kain ZN, Wang SM. Out-of-hospital auricular acupressure in elder patients with hip fracture: A randomized double-blinded trial. *Acad Emerg Med* 2006;13:19–23.
19. Kober A, Scheck T, Greher M, et al. Prehospital analgesia with acupressure in victims of minor trauma: A prospective, randomized, double-blinded trial. *Anesth Analg* 2002;95:723–727.
20. Kober A, Schubert B, Bertalanffy P, et al. Capnography in non-tracheally intubated emergency patients as an additional tool in pulse oximetry for prehospital monitoring of respiration. *Anesth Analg* 2004;98:206–210.
21. Lang T, Hager H, Funovits V, Barker R, Steinlechner B, Hoerauf K, Kober A. Prehospital analgesia with acupressure at the *Baihui* and *Hegu* points in patients with radial fractures: A prospective, randomized, double-blind trial. *Am J Emerg Med* 2007;25:887–893.
22. Bertalanffy P, Hoerauf K, Fleischhackl R, et al. Korean hand acupressure for motion sickness in prehospital trauma care: A prospective, randomized, double-blinded trial in a geriatric population. *Anesth Analg* 2004;98:220–223.
23. Dincer F, Linde K. Sham interventions in randomized clinical trials of acupuncture—a review. *Complement Ther Med* 2003;11:235–242.
24. Kaptchuk TJ, Stason WB, Davis RB, et al. Sham device v inert pill: Randomized controlled trial of two placebo treatments. *BMJ* 2006;332:391–397.
25. Kaptchuk TJ, Kelley JM, Conboy LA, et al. Components of placebo effect: Randomized controlled trial in patients with irritable bowel syndrome. *BMJ* 2008;336:999–1003.
26. Jonas WB. Directions for research in complementary medicine and bioterrorism. *Altern Ther Health Med*. 2002;8:30–31.
27. Jonas WB, Levin JS. *Essentials of Complementary and Alternative Medicine*. Lippincott Williams & Wilkins, Philadelphia, PA. 1999.
28. Lewith, GT, Walach, H, Jonas, WB. *Clinical Research in Complementary Therapies*, 2nd ed. London: Elsevier, 2011.
29. Haake M, Müller HH, Schade-Brittinger C, et al. German Acupuncture Trials (GERAC) for chronic low back pain: Randomized, multicenter, blinded, parallel-group trial with 3 groups. *Arch Intern Med* 2007;167:1892–1898.
30. Scharf HP, Mansmann U, Streitberger K, et al. Acupuncture and knee osteoarthritis: A three-armed randomized trial. *Ann Intern Med* 2006;145:12–20.
31. Molsberger AF, Schneider T, Gotthardt H, Drabik A. German Randomized Acupuncture Trial for chronic shoulder pain (GRASP)—a pragmatic, controlled, patient-blinded, multi-centre trial in an outpatient care environment. *Pain* 2010;151:146–154.
32. Niemtzow RC, Gambel J, Helms J, Pock A, Burns SM, Baxter J. Integrating ear and scalp acupuncture techniques into the care of blast-injured United States military service members with limb loss. *J Altern Complement Med* 2006;12:596–599.
33. Spira A. Acupuncture: A useful tool for health care in an operational medicine environment. *Mil Med* 2008;173:629–634.
34. Niemtzow RC, Burns SM, Cooper J, Libretto S, Walter JAG, Baxter J. Acupuncture clinical pain trial in a military medical center: Outcomes. *Med Acupunct* 2008;20:255–261.
35. NIH Consensus Conference. NIN Consensus Development Panel on Acupuncture. *JAMA* 1998;280:1518–1524.
36. Langevin HM, Wayne PM, Macpherson H, Schnyer R, et al. Paradoxes in acupuncture research: Strategies for moving forward. *Evid Based Complement Alternat Med* 2011;2011:180805.

Address correspondence to:
 Emmeline Edwards, PhD
 Division of Extramural Research
 National Center for Complementary and
 Alternative Medicine (NCCAM)
 6707 Democracy Boulevard II, Suite 401
 Bethesda, MD 20892 (Courier Service 20817)
 E-mail: edwardse@mail.nih.gov

Appendix A. DoD–NCCAM–NIH Workshop on Acupuncture for Treatment of Acute Pain Attendee List

<i>Name (Last, First)</i>	<i>Agency</i>
Ahn, Andrew	Massachusetts General Hospital Martinos Center for Biomedical Imaging
Arnold, Julia	NIH
Baxter, Col John	USAFR, Director Pentagon Flight Medicine Clinic Medical Acupuncturist
Bayat, Ahmad	NIH
Belard, Jean-Louis	TATRC, DoD
Berger, Ann	NIH
Berman, Brian	University of Maryland, School of Medicine Center for Integrative Medicine
Birkle, Dale	NIH
Bonakdar, Robert	Scripps Center for Integrative Medicine
Brackna, Christina	NIH
Briggs, Josephine	NIH
Bryce, Col Louise	USAF MC Research Medical Acupuncturist
Buchheit, Caitlin	TATRC, DoD
Burns, COL Steven	Andrews AFB, Medical Acupuncturist
Bushnell, M. Catherine	Alan Edwards Centre for Research on Pain, McGill University
Cardin, Sylvian	TATRC, DoD
Caughman, Cyndi	NIH
Cherkin, Dan	Group Health Research Institute
Coeytaux, Remy	Duke University School of Medicine
Colloca, Luana	NIH
Dubner, Ron	University of Maryland Dental School
Duffy, Linda	NIH
Dusek, Jeff	Allina Health System
Edwards, Emmeline	NIH
Friedl, COL Karl	TATRC, DoD
Gallaway, COL Kevin	Army
Glowa, John	NIH
Goldrosen, Martin	NIH
Gover, Tony	Army
Greene, Anita	NIH
Hammerschlag, Richard	Oregon College of Oriental Medicine
Harris, Richard	Oregon College of Oriental Medicine
Helms, Joseph	Medical Acupuncturist
Hickey, Anita	Senior USN Medical Acupuncturist
Hopp, Craig	NIH
Huntley, Kristen	NIH
Iadarola, Michael	NIH
Johnson, Laura-Lee	NIH
Jonas, Wayne	Samueli Institute
Kalyanaraman, Nilesh	NIH
Kaptchuk, Ted	Harvard Medical School
Khalsa, Partap	NIH
Killen, Jack	NIH
Kozel, Peter	NIH
Kuffman, Robert	Captain, USN MC, Intrepid
Lillis-Hearne, COL Pat	Army
Lixing, Lao	University of Maryland School of Medicine Center for Integrative Medicine
Lohman, Karin	NIH
Longhurst, John	University of California, Department of Medicine
Nahin, Richard	NIH
Niemtzow, Richard	CAM Consultant USAF Surgeon General
Niemtzow, Songxuan Zhou	Acupuncturist
Ordman, Joan	NNMC Medical Acupuncturist
Perrineau, Devona	NIH
Peterson, Charles	TATRC, DoD
Petri, Col Richard	MEDCOM WBAMC
Pock, Col Arnyce	USAF MC, USUHS Medical Acupuncturist
Roesel, Tom	Army
Schmidt, Martina	NIH
Sherman, Karen	Group Health Research Institute
Shryer, Amber	TATRC, DoD
Smith, Wendy	NIH

(continued)

APPENDIX A. (CONTINUED)

<i>Name (Last, First)</i>	<i>Agency</i>
Sorkin, Barbara	NIH
Vickers, Andrew	MSKCC
Walter, Joan	Samueli Institute
Wayman, Dawn	NIH
Weber, Wendy	NIH
Witt, Claudia	Institute of Social Medicine, Epidemiology and Health Economics Charité University Medical Center, Berlin, Germany
Zubieta, Jon-Kar	University of Michigan