Current Indications of Acupuncture

Moderated by Brian Berman, MD

Discussants: Joseph Helms, MD; Gary Kaplan, MD; Lixing Lao, PhD, LAc

DR. BERMAN: I’m Brian Berman, director of the University of Maryland Center of Integrative Medicine and Professor of Family and Community Medicine at the University of Maryland, School of Medicine.

Acupuncture (a traditional Chinese medical practice systematically used for over 2000 years) involves insertion of thin stainless steel needles into specific points on the body to facilitate recovery and good health. This practice was first brought to Europe in the 17th Century, and the first journal article on acupuncture appeared in the 1820s. Not until recently has acupuncture been widely accepted because of the clash of east versus west paradigms.

Scientific advances in acupuncture research, coupled with the side effects of treating pain by conventional drugs, have dramatically promoted the use of acupuncture in the last 20 years. It is estimated that over 1 million practitioners (outside China) administer acupuncture treatments for chronic pain. Of these practitioners, over 300,000 are physicians. An estimated 3 million American adults receive acupuncture treatments each year, and chronic pain is the most common presentation.

One of the most significant events in the 1990s for acupuncture was the decision taken by the US Food and Drug Administration in March 1996 to reclassify the legal status of acupuncture as safe and effective medical devices.

Further, in November 1997, there was a consensus conference on acupuncture by the National Institutes of Health. This was a 2.5-day conference conducted to evaluate the scientific and medical data on the uses, risks, and benefits of acupuncture for a variety of conditions. The findings after reviewing approximately 2300 studies stated that “Promising results have emerged, for example, showing efficacy of acupuncture in adult postoperative and chemotherapy nausea and vomiting and postoperative dental pain.”

There are other conditions such as stroke rehabilitation, headache, tennis elbow, osteoarthritis, lower back pain, carpal tunnel syndrome, and asthma, for which acupuncture may be useful as an adjunct treatment or could be included in a comprehensive management program. Although many issues remain to be clarified, there is sufficient evidence to prove the value of acupuncture in order to expand its use in conventional medicine and encourage further studies of its physiology and clinical value.

Since the consensus conference in 1997, there has been a huge increase in the number of scientific studies conducted on acupuncture. The Cochrane Collaboration’s database includes now 6035 clinical trials and 53 systematic reviews on acupuncture in their database. This roundtable today will focus on the current indications for acupuncture, and we will discuss how it is used in clinical settings, its safety issues and clinical evidence, and how it works.

The other participants are Dr. Joseph Helms, Dr. Gary Kaplan, and Dr. Lixing Lao. Dr. Helms is the founding president of the American Center for Integrative Medicine.

ABSTRACT

The discussion focused primarily on: 1) The history of acupuncture; 2) how acupuncture is used in clinical settings; 3) safety issues surrounding use of acupuncture; 4) the clinical evidence of effectiveness and efficacy of acupuncture; and 5) the mechanisms through which acupuncture works. Med Roundtable Gen Med Ed. 2014;1(4):335–344.

Discussion held on October 9, 2012.
Scientific advances in acupuncture research, coupled with the side effects of treating pain by conventional drugs, have promoted the use of acupuncture dramatically in the past 20 years. It is estimated that over 1 million practitioners outside China administer acupuncture treatments for chronic pain. Of these practitioners, over 300,000 are physicians.

To begin this discussion, Dr. Helms, can you describe for us the different types of acupuncture, training, and how acupuncture is used in a clinical setting?

Dr. Helms: Thank you, Dr. Berman. Acupuncture is relatively new in the collection of American medical disciplines. It has been in constant evolution since President Nixon’s visit to China in 1972. This evolution is driven by public interest and demand as well as scientific evidence of its mechanism and clinical value.

The tradition, with which I’m most familiar with, is known as medical acupuncture. Medical acupuncture would best be described as a hybrid approach combining our understanding of acupuncture on pain to the endogenous opioid peptide cascade, which is currently being reinforced through functional magnetic resonance imaging studies that confirm an intracranial response to peripheral needling.

The 1997 Consensus Development Conference report that endorsed a handful of acupuncture applications was based on the quality of research design to evaluate acupuncture’s impact on different problems, rather than on the actual practice of acupuncture. Since that paper, over 400 randomized control trials have been published in peer review journals internationally. These studies demonstrate the favorable impact of acupuncture on a wide spectrum of medical problems, including, but not limited to, pain.

There are many different styles of acupuncture. This discipline has evolved through multiple cultures over the last 2000 years. Each culture and era of its blossoming has contributed its enduring quality and approach. Many of these styles of acupuncture were retained only in family traditions, while others were propagated nationally. It is only in the late 20th century and beginning of the 21st century that we have had the privilege to access many of the family and most of the national traditions of acupuncture training and practice.
Many pain problems can be effectively managed with acupuncture alone or as an adjunct to conventional approaches. Functional or psychosomatic problems can also frequently be addressed using acupuncture in ways not possible through pharmaceutical approaches. Acupuncture covers a broader range of clinical applications than simple neuromusculoskeletal pain or psychosomatic issues. It can be creatively integrated into much of the spectrum of modern medicine."

Joseph Helms

DR. BERMAN: I think in the past, auricular acupuncture was also used for problems of addiction but I don’t know if it’s still being used for this purpose.

DR. HELMS: There are several widely used acupuncture point combinations that have been shown to be useful in assisting a multidisciplinary approach to substance abuse problems, referred to as the “NADA protocol” that was developed by Michael Smith, MD. There is also a 5-point formula called battlefield acupuncture that is useful in dealing with acute traumatic pain.

DR. BERMAN: Thank you, Dr. Helms. Dr. Kaplan and then Dr. Lao, could you comment about what’s being done in clinical settings and how acupuncture is used to treat certain diseases beyond what Dr. Helms has just explained?

DR. KAPLAN: We do a great deal of work for the treatment of pain and find acupuncture to be extremely effective for conditions such as headaches, back pain, and neck pain. We also find it useful for the treatment of peripheral neuropathies. In addition, because we deal with many chronic pain patients, we also see a lot of psychosomatic issues comorbid with the chronic pain. Acupuncture has proven to be very helpful as an adjunctive therapy dealing with the psychosomatic components that we see associated with chronic pain.

In my practice, approximately 20% of our pain population has post-traumatic stress syndrome, while approximately 60% has comorbid anxiety disorders or major depressive disorders. Acupuncture has been particularly unique as a therapeutic modality because it addresses both the pain and the psychological component of an individual’s illness at the same time. We’re able to talk about the totality of the classics, but rather is an extraction that can be taught and absorbed by the western community. The Traditional Chinese Medicine approach covers internal medicine problems as well as pain problems.

Two additional, commonly used subdivisions of acupuncture are auricular acupuncture and Chinese scalp acupuncture. Auricular acupuncture was developed in France in the 1950s and 1960s and uses points exclusively on the ear to influence pain and organ function. Chinese scalp acupuncture is a recent development in Chinese medicine. It involves placing needles in the scalp overlying the cortical surfaces that relay pain signals.

DR. BERMAN: Could you elaborate on auricular acupuncture a little more and on what it is used for?

DR. HELMS: Auricular acupuncture is the least complex and most easily learned approach to acupuncture. It can be effective either as a standalone treatment or as an adjunct to body acupuncture. The scientific foundation of auricular acupuncture involves the ear’s complex innervation that links it to all 3 embryologic germ levels. Thus, with neurological representation of endoderm, mesoderm, and ectoderm, the ear manifests a homunculus of all body parts. Ear points that correspond to painful or disturbed structures demonstrate increased electrical conductivity and thereby allow the ear to serve as a diagnostic tool and a therapeutic signal.

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of the individual as opposed to segmenting them into psychiatric versus pain versus sleep issues. From an acupuncture perspective, these conditions are not separate issues but different manifestations of a pattern of disharmony in the individual.

**DR. LAO:** I agree with Drs. Kaplan and Helms. In my practice, I see patients with a variety of complaints. In addition to pain, they also experience menopause disorders, depression, and attention deficit disorder (ADD) (in children). A wide variety of diseases can be treated by acupuncture. Evidence of the effectiveness of acupuncture for the treatment of pain has recently been published by Vickers.4

**Individual raw data show the full area of musculoskeletal pain, which includes neck pain, low back pain, headaches (migraine and tension headaches), osteoarthritis in the knees, and shoulder pain. There is a significant difference between acupuncture and conventional treatment in terms of their therapeutic effectiveness. There was also a significant difference between acupuncture and sham acupuncture, ie, placebo needles at points on the body that are not thought to be acupuncture points (off site points). Although the benefits were modest, they were highly significant.**

Dr. Berman, do you also want me to cover a little bit about the side effects or shall we save that for later?

**DR. BERNMAN:** Let’s stick to the clinical use first, and then we’ll go to the side effects.

**DR. KAPLAN:** I’d like to chime in here. I’m boarded in family medicine and pain medicine and started my clinical practice in a general medical setting. As my practice evolved, I began seeing a greater number of individuals suffering with chronic pain and illness issues.

"Overall, the neurophysiological evidence shows that acupuncture treatments affect the central nervous system in ways that are beneficial, long lasting, and unique to true acupuncture treatments. The neurophysiological evidence is also beginning to explain why we see different degrees of clinical effectiveness of acupuncture in conditions as diverse as gastrointestinal disorders, pain, and psychiatric conditions."  

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Gary Kaplan

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Over the last 30 years, acupuncture has heavily influenced my approach to patient care. Acupuncture is not simply a tool but a philosophy of care that has greatly enriched my western medical training. At times, when treating a patient, I believe the prism of a western approach will be more effective; there are also times when I rely exclusively on an acupuncture approach, but more commonly, I integrate the two in designing and implementing a care program.

Pain can be very effectively managed with acupuncture alone or as an adjunct. Many so-called functional or psychosomatic problems can be more effectively addressed using acupuncture in place of pharmaceutical agents. Likewise, the conventional approaches to organic problems can be reinforced and facilitated with acupuncture treatment.

Acupuncture covers a much broader range of clinical applications than simple neuromusculoskeletal pain or psychoemotional issues. It really covers the full spectrum of medicine.

**DR. BERNMAN:** Thank you, Dr. Kaplan. There are 2 nonpain conditions that I believe we haven’t mentioned yet. First, there’s nausea and vomiting due to chemotherapy or after operations, and second, chronic obstructive pulmonary disease (COPD) breathlessness. I was wondering if the three of you have encountered patients with these symptoms and employed acupuncture to control these conditions?

**DR. KAPLAN:** We have used acupuncture successfully in women with hyperemesis gravidarum. Most of the medications are contraindicated because of the potential harm to the fetus. Acupuncture has been successful in at least providing these women with some level of relief in treating this condition.

I don’t have experience with acupuncture therapy for postoperative nausea/vomiting. We have used it a little bit in nausea/vomiting associated with chemotherapy,
and again, we’ve been able to reduce the amount of medications that the patients require in order to control it; in some cases, we’ve actually been able to eliminate the need for medications.

Further, I want to go over what Dr. Helms was talking about—the importance of integrating acupuncture into a comprehensive treatment program. It is sometimes the main therapeutic modality that we use, but on many occasions, it is integrated into our medication regimes. In a comprehensive approach, we may use it in conjunction with physical therapy, and we will also be probing trigger points. We may also do prolotherapy with the patients.

Acupuncture gives us the ability to treat a wider range of conditions with fewer medications. We are frequently able to address irritable bowel syndrome (IBS), sleep disorders associated with the medical conditions, as well as the psychiatric conditions I was talking about earlier. Acupuncture is a beautiful adjunctive therapy and sometimes can be used as the sole therapeutic approach.

DR. BERMAN: In general, we’re now talking about acupuncture being part of a comprehensive approach to a number of chronic disorders.

DR. KAPLAN: That’s absolutely correct. You want to use all of the tools you have available, and acupuncture is a very powerful therapeutic modality in the treatment of these conditions.

DR. LAO: One of the nonpain areas that I think people should consider using acupuncture as a therapy is infertility. Many women now come to the clinic, particularly after the publication of the enhanced success rate of in vitro fertilization (IVF) in women receiving acupuncture treatment. Even those patients who elect not to go through IVF come for acupuncture treatment to enhance their chances of getting pregnant.

DR. BERMAN: Dr. Lao, is there evidence to support acupuncture for infertility?

DR. LAO: There’s a paper that was published a couple years ago through our center. The authors show a higher success rate of conventional IVF procedure when combined with acupuncture than with sham control. Current studies give clear evidence of the benefits of acupuncture to IVF patients.

DR. BERMAN: With the breathlessness COPD I was referring to, there was a study in the Archives of Internal Medicine just this past June 2012, which was a very well-done clinical trial aimed at studying COPD and using acupuncture in addition to conventional care, that showed clear outcomes of the benefits of acupuncture in this particular condition.

Dr. Helms, you have experienced acupuncture in the military setting. Can you talk a little bit about that?

DR. HELMS: In the last 5 years, 3 branches of the US Military have shown interest in pursuing acupuncture training for physicians to provide these services to their population. This interest reflects what’s happening in the civilian population and is more intensively motivated by the report of the Army’s pain management task force that identified some severe short-comings in managing acute and chronic pain. The feedback we’ve received from the military physicians we’ve trained has been very rewarding. The bulk of their treatments are for pain, ranging from headache to cervical, lumbar, and peripheral pain. Much of this pain is caused by the weight of their 75-pound protective gear, which they wear no matter where they are in the world, and of course, the physical trauma of battle. Interestingly, an almost equal percentage of treatments for active duty service members are for psychoemotional problems (anxiety, insomnia, depression, acute stress, and chronic stress) as for pain and physical trauma.
DR. BERMAN: Let me move on to the next subtopic. Dr. Lao, can you talk to us about how safe acupuncture is?

DR. LAO: There are few reported cases of complications in the English literature from 1965 to 1999, a 35-year span. There were a total of 202 case reports, which is about 5–6 cases per year.10 I have completed 2 reviews of case reports on adverse events associated with acupuncture. One was published in 200310 and the other one is accepted for publication.11 Events are divided into complications and adverse reactions. Complications such as injured organs or infections occur if acupuncture is not carefully performed. Adverse reactions include syncope and allergic reaction.

Infections constituted 50% of all complications. Needle infections may cause hepatitis. However, since the late 1980s, acupuncturists started using disposable needles, resulting in lower incidence of hepatitis and other infections.10 In recent years, another infection emerged that involves many different invasive procedures in medical settings such as methicillin-resistant Staphylococcus aureus (MRSA). This is likely due to the unsanitary conditions of these clinical settings, such as the use of contaminated disinfectant. It’s not the acupuncture needle itself that caused infection.

A larger survey12 showed that approximately 7% to 8% of the adverse events were classified as mild. These events include local site bleeding, pain in local needling site, nausea, or light-headedness. The occurrence of these mild adverse events is very low especially in the context of the large numbers of patients attended to acupuncture clinic every year.

In the last 10 years, 308 cases of side effects were noted from 26 countries.11 In the United States, only 17 cases have been reported, which is a very small percentage. I believe that this is due to extensive professional licensing requirement that is called Clean Needle Techniques (CNT) training. This requirement has dramatically decreased the risk of unnecessary side effects.

Other types of adverse events such as organ and tissue injuries are associated with knowledge of anatomy. Therefore, proper training of the acupuncturist could help reduce the occurrence of side effects due to acupuncture.

DR. BERMAN: From these prospective studies,10–12 we can conclude that serious adverse events are very rare with acupuncture and that there is, depending on the surveys, a 2% to 7% probability of occurrence of a mild side effect such as local site bleeding or occasional dizziness or localized pain to the area. Is there anything else on safety that either, Dr. Kaplan or Dr. Helms would like to add?

DR. HELMS: In addition to reinforcing that acupuncture is a very safe and forgiving therapeutic approach, I’d like to discourage readers from concluding that useful indications for acupuncture in medical practice are limited to what is published in the evidence-based literature. Acupuncture has been used for simple and complex problems by responsible practitioners in oriental and occidental cultures for much longer period than we have been documenting its efficacy. Acupuncture comes from a long tradition of the practice of medicine, albeit in cultures and eras quite distant from ours. Our hybrid medical acupuncture allows remarkable creativity in the hands of well-trained practitioners, to treat many problems that are not included among those already studied in the pharmaceutical model.

DR. BERMAN: I think that’s a very important point, but let’s talk a little bit about the research first, and then go back to this when we’re putting the research into the context of clinical practice. How should we take this into account?

DR. KAPLAN: Let’s briefly look at the clinical research, and then talk about some of the problems that we run into with research and what the research shows us in terms of how to better study procedures such as acupuncture, because studying procedures is different from studying drugs. The clinical studies roughly fall into 2 categories: effectiveness studies and efficacy studies, and many studies overlap and attempt to do both.

An effectiveness study looks at the extent to which a drug or procedure achieves its intended effect in the usual clinical setting. In these circumstances, you’re randomizing acupuncture against something such as a wait list control or usual care such as physical therapy or medications.

In 2009, a Cochrane database review studying acupuncture for prophylaxes of migraine showed that acupuncture was at least as effective, and possibly more effective, than prophylactic drugs with fewer adverse effects.13

In 2012, Andrew Vickers and his colleagues4 performed individualized patient data meta-analysis of 17,922 patients with a variety of back, neck, shoulder,
Efficacy is the extent to which a drug or procedure has the ability to bring about its intended effect under ideal circumstances, that is, acupuncture compared to a placebo. In the Vickers study,4 Vickers looked at the efficacy of acupuncture in the treatment of chronic pain and again concluded that true acupuncture was statistically slightly more efficacious than sham. Although this was not a big effect, it was nonetheless statistically significant.

From the 2012 Cochrane database review of IBS14 it was concluded that acupuncture was not efficacious as compared to a creditable sham, but there were several effectiveness trials where acupuncture tested better against 2 antispasmodic medications, which have some effect on both the severity and quality of life in patients with IBS.

While the Vickers study reported the efficacy as well as effectiveness of acupuncture, the IBS trial did not find any efficacy, when compared to the placebo, but did find evidence of the effectiveness of acupuncture.

There’s another trial that came out this year in Physical Medicine and Rehabilitation by Yao et al15 that studied the efficacy of acupuncture over sham for the treatment of carpal tunnel. It was found that both sham and true acupuncture were helpful in the treatment of carpal tunnel, but failed to demonstrate a statistically significant difference between the verum and sham acupuncture groups.

What is particularly interesting about this study is that the natural history of carpal tunnel suggests that you will notice a 20% to 40% improvement over time. However, this study showed an 88% statistically significant improvement in both the true and sham acupuncture groups, which was maintained over 3 months of follow-up after the treatments ended.

The question that arises now is how you reconcile all of this, because it seems that the first piece of information that you come up with is that the sham may actually be a different form of active treatment. There’s an interesting study by Richard Harris and others in neuroimaging that was published in 2009.16 Harris’ team looked at the effects of true and sham acupuncture on the mu-opioid receptors in the central nervous system (CNS) using positron emission tomographic scanning in patients with fibromyalgia. Prior studies in patients with fibromyalgia have demonstrated increased levels of endogenous opioids in the cervical spinal fluid with decreased sensitivity in the mu-opioid receptors in the CNS regions known to be associated with the modulation of pain.

In the Harris study, the authors found that true acupuncture therapy evoked both short- and long-term increases in mu-opioid-binding potential receptors in the multiple pain areas and sensory processing areas associated with pain regulation. This was associated with clinical reports of pain reduction on the part of the subjects.

In the sham group, they also reported reduction in pain, though less than that in the true acupuncture group, and the positron emission tomographic scan showed no effect on the sensitivity of the mu-opioid receptors. The binding potential of these receptors did not improve as they did with the acupuncture treatments.

We know from prior studies that both true and sham acupuncture seem to increase the release of endogenous opioids, and we see that effect occurring in the ascending pathways and a segmental effect occurring in the spinal cord as well as in the descending modulating pathways mediated via dynorphins serotonin and norepinephrine. However, the effects of true acupuncture on the mu-opioid binding sensitivities are different from that of sham acupuncture.

In addition to this, we have imaging studies that have been conducted since the 1990s, and a recently published meta-analysis by Huang et al,17 which showed that while there is a problem with heterogeneity of these studies, they were able to conclude that the brain response to acupuncture encompasses a broad network of regions consistent with somatosensory affective and cognitive processing.

Overall, the neurophysiological evidence shows that acupuncture treatments affect the CNS in ways that are beneficial, long lasting, and unique to true acupuncture treatments. The neurophysiological evidence is also beginning to explain why we see different degrees of clinical effectiveness of acupuncture in conditions as diverse as gastrointestinal disorders, pain, and psychiatric conditions.

We have a lot more to learn and, far from being discouraged by this conflicting evidence in the literature, we should be excited by how
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I think you mean that when we’re talking about evidence-based medicine, it’s not just about the efficacy shown by randomized control trials. There’s a wider range of methodologies and diseases to consider, depending on the question being asked. This is true of all medicine, including acupuncture, and if we narrow it down too much, we may fail to reap the benefits of using a very valuable tool as part of medicine.

DR. KAPLAN: I think you’re absolutely correct. The other thing that we need to keep in mind is that the evidence-based research itself is a very limiting concept because we keep finding new mechanisms and understanding new subtleties about how the nervous system is working, how our physiology works, and then we’re able to go back and say, “Ah, that’s the mechanism via which this is happening.” This whole topic about mu-opioid receptors is actually a breakthrough in terms of understanding how acupuncture may affect the CNS, which is unique and different from the way that sham does.

DR. BERMAN: What do you think are the cutting-edge research questions that still need to be answered as we go forward, questions that could not only inform us of how acupuncture works but could also affect clinical practice?

DR. KAPLAN: One of the areas that I’ve been particularly focused on is the microglial cells and their impact as the ultimate transducers between psychological stress, which gets translated into neurologic damage; and physical stress such as traumatic brain injury; as well as infectious stress, which also creates problems with neuroinflammation and neurodegeneration in conditions such as chronic pain and chronic illness.

Clinical Implications

► Acupuncture is extremely effective for conditions such as headaches, back, and neck pain.

► Acupuncture is very helpful as an adjunctive therapy dealing with the psychoemotional components that are associated with chronic pain.

► Acupuncture is unique as a therapeutic modality because it addresses both the pain and the psychological component of a given individual’s illness at the same time.

► Acupuncture has applications as a therapy for infertility.

► Serious adverse events are very rare with acupuncture, a 2% to 7% probability of occurrence of a mild side effect such as local site bleeding or occasional dizziness or localized pain to the area.

► Acupuncture’s effects on microglia may provide more insight into how acupuncture works.
We have seen evidence that acupuncture is actually neuroregenerative in some circumstances, certainly from some of the carpal tunnel studies that have been performed. We know that the microglia are involved in neuroregeneration; therefore, studying the effects of acupuncture on microglia may give us much more insight into how acupuncture works. This would be one area that I think should be focused on.

DR. BERMAN: Dr. Helms or Dr. Lao, any questions you think still need to be answered that can really make a difference?

DR. LAO: I agree with everything you have already said, but I think I’ll add one point: we need more translational studies on how to apply the scientific information to our daily practices in order to enhance the effectiveness of acupuncture treatment. We did some studies in which the effectiveness of a combination of conventional medication and acupuncture was evaluated. We found that the effectiveness of the combined therapy was much higher than that of acupuncture or the medication alone. Maybe, in the future, the research should be designed to answer the question of whether acupuncture reduces the side effects of a medication, resulting in enhanced effectiveness of both medicine and acupuncture.

DR. BERMAN: I would add one point that goes along with that: we need to get a better idea of the responders and nonresponders to acupuncture. We could begin to address this by setting up some pragmatic clinical trials with the idea of comparative effectiveness research in actual settings of clinical practice as well as cost effectiveness. Further, we could determine who responds, and we can include imaging and genomics assessments as part of the biomarkers that we’re analyzing.

DR. KAPLAN: I completely agree with you. I think that’s a challenge that we need to potentially take on in the future, but it’s something to be looking towards as we’re going to have to be more cost effective and more cost conscious in our treatment of a variety of diseases. I think acupuncture has a significant role to play here but we are not ready to perform those studies yet. We need to start to think about them and how they can be accomplished.

DR. HELMS: In the past, we have thought of acupuncture as a treatment for chronic conditions, but one of the biggest problems we face in the military today is trauma. It could be possible to compare management outcomes at military facilities that have integrated acupuncture into their trauma treatment with those that have not.

DR. BERMAN: Here is where the military comes into play. They have proposed a move towards expanding availability of acupuncture immediately following trauma and then follow that through with intermediate and long-term care facilities. If this approach succeeds, it would create an environment in which those issues of acute, subacute, and chronic consequences of trauma could be evaluated.

DR. LAO: In ancient literature, early acupuncture was largely used for emergency medicine, particularly in the ancient times when patients were unconscious or in conditions such as fainting or convulsions where they could not be treated with oral medicines. There is a large body of ancient literature that has documented this use.

DR. BERMAN: I want to thank all of you for participating in this discussion; it’s been a real pleasure.
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REFERENCES


