FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ASSESSMENT OF ANALGESIC TREATMENT OF CHRONIC PAIN: A SCIENTIFIC WORKSHOP

Wednesday, May 30, 2012

1:00 p.m. to 5:30 p.m.

Natcher Auditorium

Natcher Conference Center

NIH Campus

45 Center Drive

Bethesda, Maryland 20892

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P R O C E E D I N G S

(1:06 p.m.)

Opening Remarks – David Rappaport

DR. RAPPAPORT: Good afternoon. We'll go ahead and get started now. If you'll take your seats, please.

I'm Bob Rappaport. I'm the director of the Division of Anesthesia, Analgesia and Addiction Products at the FDA, and I'd like to welcome you all here today. This is the FDA Scientific Workshop on the Pharmacologic Treatment of Chronic Pain.

I'd like to thank the NIH Pain Consortium, and Dr. Linda Porter in particular, for partnering with us on this three-day meeting and for allowing us to hold our workshop here at Natcher. The Pain Consortium symposium, presentations and discussions from yesterday and this morning, for those of you who were lucky enough to hear them, were excellent. And I think they really sort of set the stage for our discussions this afternoon and tomorrow.

The question of whether opioids should be

used to treat chronic non-cancer pain is not only a highly controversial one; it's also a critically important one, based on two intimately connected public health issues in this country: the need for improvement in the treatment of pain and the significant risks associated with chronic opioid use.

The increasing misuse and abuse of prescription opioids, which are resulting in a clearly unacceptable incidence of addiction, overdose and death, is a major public health problem that numerous stakeholders, including many of you here in the room today, have been trying to address in a variety of ways for over a decade now. While we may not all agree on the best ways to address this problem, I think we can all agree that we must continue our efforts to find interventions that will truly make a difference.

That said, the risks associated with chronic opioid use are not the focus of this workshop, although they clearly underlie the need for this public discussion. We're here today and tomorrow

to discuss what is known about the effectiveness of opioid treatment for chronic non-cancer pain and the place of opioid analgesics in the overall armamentarium of pain treatment options.

To that end, we have put together what we hope will be a spectrum of presentations and panel discussions that will discuss any data that are available to demonstrate that opioids are effective in chronic non-cancer pain and any data that are available to demonstrate that opioids are not effective in chronic non-cancer pain, and to identify what additional research is needed to fill in the data gaps in order to allow these drugs to be used as safely and as effectively as possible.

Of course, understanding the role of opioids in the treatment of chronic non-cancer pain can only be fully realized when put into the context of the alternative treatments that are available, both pharmacologic and non-pharmacologic. Therefore, we will also be reviewing and discussing the efficacy data for other pharmacologic treatments and at a high level the data regarding non-pharmacologic

interventions.

This is a scientific workshop, not an advisory committee meeting. The FDA convened this workshop to provide a public forum for all stakeholders to understand the state of the science. We are not here to receive advice on regulatory matters.

We'll begin the workshop this afternoon with a panel on the scientific underpinnings of pain, and that will be followed by a panel on the epidemiology of chronic pain. Finally, today we will have our open public hearing session, during which a large number of speakers who pre-registered for that session will present their concerns related to the topic of our workshop.

Tomorrow morning, we'll begin with a panel that really is key to this workshop. Four experts in the study and treatment of pain will review the data for us, and those presentations will be followed by comments from an expert group of discussants, and then a discussion among all of the panelists, and a question and answer period for the

audience.

Our second panel tomorrow will be an opportunity to hear from some folks who are on the front line of treating and advocating for patients with chronic pain. We will round out the workshop with a lessons learned panel, consisting of all of the moderators, speakers, and discussants from both days. Hopefully, by that point, we will be ready to come up with a consensus on a research agenda.

As I've already noted, the use of opioid analgesics for treating chronic pain is quite controversial, and the devastating impact that misuse and abuse have had in this country have left many with strong feelings about these drugs. There is also another public health issue, the undertreatment of chronic pain in the U.S., about which many people have strong feelings and legitimate concerns.

Nevertheless, it's essential that if we're going to achieve our important objective today of understanding what is known about the efficacy of opioid analgesics for chronic non-cancer pain,

we'll need to stay focused on the topic at hand and avoid the interference that can occur when people are moved by emotion. Therefore, we're asking that everyone in this room today follow a few simple rules.

Please do not speak unless you are recognized by Dr. Throckmorton, me, or the moderator for a particular panel. We will do our best to allow ample time for questions from the audience according to the agenda. If you are recognized, please use your limited time efficiently, and if asked to yield the floor to the next person waiting to ask a question, please do so. Finally, and perhaps most importantly, while there are clearly strong opinions and powerful emotions tied to the issues under discussion, we can only have a successful workshop if everyone in this room treats each other with the respect and courtesy that we are all due. Please allow people to have their say without expression of disagreement during that time. We'll do our best to assure that all points of view are

considered and as many voices as possible are heard.

So before I take any additional time away from these extremely important and relevant discussions, I'd like to thank some of the people who've worked so diligently to make this event happen. First, I'd again like to express the FDA's gratitude to our NIH partners for sharing their work, and their knowledge, and their facilities.

Next, I'd like to mention Dr. Janet Woodcock, director of the Center for Drug Evaluation and Research at FDA, and my co-chair for this meeting, Dr. Doug Throckmorton, CDER's deputy director, who have provided their support and encouragement to this process from the beginning, and we wouldn't be here today without that support.

I'd also like to thank the pain team from my division who helped in the preparations, reviewed much of the literature themselves, and provided valuable insights as we planned the workshop. And a special thanks to Dr. Pamela Horn for her work reviewing and preparing a presentation on the

recently published guidelines on opioid use and the treatment of chronic non-cancer pain that you'll be hearing tomorrow. And we are enormously grateful to the moderators, speakers, and discussants, who you'll be hearing from on both days. Each one of them has spent a good deal of time preparing for this meeting. And the speakers in particular have done an outstanding job of reviewing literature and preparing what I think you will find our excellent presentations.

Finally, there are a few people who have worked tirelessly on the preparations and logistics for this workshop, Lieutenant Commander Matthew Sullivan from my division, and Ms. Mary Gross, from CDER, and her team have put in countless hours to assure a successful meeting, and their professionalism and commitment are deserving of our thanks.

At this time, I am going to turn the podium over to Dr David Thomas from the National Institute of Drug Abuse, who will be moderating our first panel on the basic science of pain. Dr. Thomas is

the program officer in charge of basic science research at NIDA. He spent 10 years at NIDCR studying opiates, and he's been a member of the NIH Pain Consortium since its inception.

Moderator – David Thomas

DR. THOMAS: Thanks, Bob.

As Bob said, I'm Dave Thomas, program officer at the National Institute on Drug Abuse. NIDA is the second largest funder of pain research at the NIH. That's a surprise to some, but that's kind of why we're in the room here. And I think that this meeting's important in that it's looking -- it's important that we're at this meeting with you. It's important that you're dovetailing this with the Pain Consortium because we have two serious problems -- prescription drug abuse and pain -- in this country. The fact that we're together working on this is a very good thing.

Also, I've talked to Bob previously about this, how NIDA and the FDA are in a similar boat when it comes to prescription drug abuse and pain.

We think both are bad. We're trying to cure both, and it's tough. But again, as Bob said, the focus of this meeting is on opiates, so I'll get started with introducing the speakers.

The first session is titled, The Basic Science of Pain. The first speaker is Clifford Woolf, who is the director of the Kirby Neurobiology Center and the program of neurobiology at Children's Hospital Boston. He's a professor of neurology and neurobiology, and a member of the programs in neuroscience and immunology at Harvard Medical School, and a faculty member of the Harvard Stem Cell Institute. His pain research focuses on understanding basic mechanisms of pain and translating the results into therapeutics.

Dr. Woolf holds 15 patents, patent applications and licenses, for technology innovations in pain management. He's also received numerous awards, including the Wall medal from the Royal college of Anesthesia, and also the Javits Award from NINDS. The title of his talk is Unraveling Pain Mechanisms for Targeting Therapy.

Dr. Woolf.

(Applause.)

Presentation – Clifford Woolf

DR. WOOLF: Good afternoon. It's a real pleasure to have the opportunity to kick off this important meeting, as Bob Rappaport deals with important issues, societal issues, in terms of the treatment of pain and the consequences of the treatment, some undesired consequences of the treatment of pain.

What I would like to do this afternoon is to try and highlight some of the problems that we confront, but also the opportunities that they present if we analyze them in a constructive and scientific fashion.

Firstly, my disclosures. A lot of what I'm going to discuss has actually been reviewed in an article that I wrote with two of my colleagues earlier this year, Christian von Hehn, who is a senior post-doctoral fellow in my lab, and Ralf Baron. By an amazing coincidence, both of them graduated from Kiel University in Germany and have

never met each other. And what I will try to do today is show how the work that Ralf has been doing as part of the German neuropathic pain network is integrating with some of the approaches that we've been doing, and trying to understand the basic mechanisms that drive the generation of pain and the consequences of this for treatment.

The crux of the issue, I believe, is summarized in this slide. And this really indicates the linkage between etiological or pathological factors that act on the body to generate chronic or persistent pain. And as clinicians, we pay a lot of attention to what the etiological factors may be and also the pain conditions that they derive. And this currently forms the basis on which we make decisions about what are the most appropriate therapies for our patients.

What I'd like to emphasize is that in addition to this standard or classical approach to the diagnosis and classification of pain, we need to introduce some other factors. One is the

genotype of our patients, which plays a major role in determining how they respond to pathology and also how they respond to different therapy.

Environmental factors are also important. These three together act particularly on the nervous system to alter its function. And it is the alteration in its function, which is the driver of the pain condition. I think the important thing that we need to appreciate is these neurobiological mechanisms that produce pain are not homogenous. There's not a single switch which when activated by these three factors produces pain. There are in fact many different switches. And this is very important because our treatment act on these switches and sometimes we do not introduce to our patients the correct treatment that is targeted at the underlying mechanism that is driving that pain.

So I think there are two major issues. One is, can we identify the mechanisms and can this reveal to us what are the appropriate kinds of therapies that can act on these mechanisms to produce analgesia. And this really relates to the

issue of what are the targets that are most appropriate for the development of effective treatments for pain. I'm not going say an awful lot about that. And in fact, there is a meeting in October that's being hosted by ACTION, which will actually be at the FDA campus, which will deal very specifically with the development of novel analgesics.

What I am going to instead focus on is another issue, which is what I think is a major problem, which is the fact that not all our patients respond to a treatment. And in fact, those treatments that currently have labels for neuropathic pain typically have a number needed to treat of over four, which means that four patients need to be treated for just one of them to have a clinically meaningful reduction in pain.

So the responder rate is currently -- with the available treatment, the best available treatment, the gold standard treatment -- is about 25 percent, which means that 75 percent of patients are getting treatment and are not responding to it.

And this is I think a major issue. And the question is why is that so, and what can we do about it. And the case I'm going to try and make for you today is that if we change our view of what are the ways in which we need to try and enrich responders for therapy, based on the mechanisms that are generating the pain, there is the possibility that we may increase the responder rate by targeting appropriate therapies at particular mechanisms that are present in particular sets of patients. And in that way, we can match the treatment with the mechanism and produce a greater responder rate.

So if we just expand on this a little bit. Here are several examples of etiological factors that may drive neuropathic pain syndromes, and today I'm going to focus entirely on neuropathic pain. These may be metabolic disorders, peripheral injury to the nervous system, infections of the nervous system, and a variety of chemical toxins.

These, in combination with the genotype of the patients and environmental factors, activate a

series of changes within the nervous system, which represents the pathological or neurobiological mechanisms that result in the generation of the pain sensation. And these may include damage to the nervous system, abnormal excitability of the nervous system, changes in its synaptic transmission, changes in the balances of excitation and inhibition in the nervous system, and also changes in the fundamental connectivity of the nervous system. These then generate the syndromes that we as clinicians see, such as diabetic neuropathy, postherpetic neuralgia, HIV neuropathy, et cetera.

But what typically we do as clinicians is we try and focus on the etiology and the clinical diagnosis, but do not pay much or any attention to the individual pathophysiology. This is understandable when we didn't know much about how pain was generated. But over the last decade, in particular, there have been extraordinary advances in our understanding, in general terms, about how the nervous system functions, but also in

particular about the pathways that are engaged in the production of pain.

So in the most general sense, we are aware that our somatosensory system has two major pathways, those that mediate a low -- are activated by low-intensity stimuli and generate innocuous sensations, such as touch or pressure. And then there are a set of highly specialized, high-threshold sensory fibers, the nociceptors, which respond typically to noxious stimuli, such as intense mechanical force, extremes of temperature, or chemical irritants. And the activation of these nociceptors then activates a set of pathways, the nociceptive pathways in the nervous system that eventually leads to the activation of those cortical regions that generate the sensation of pain.

Now, if we're trying to analyze the neurobiological changes that contribute to the pain syndromes patients have with peripheral neuropathic pain, then one of the major features is actually damage to the nervous system itself. Certainly, in

order for a patient to have a diagnosis of neuropathic pain, there needs to be demonstrable damage to the nervous system. This can take place at different sites across the peripheral nervous system. This could be terminal atrophy, where the peripheral terminals of sensory fibers degenerate, or there could be frank axonal degeneration. But in both of these cases, the consequences of this damage to the nervous system is going to be a loss of sensation. So these cause negative symptoms, such as numbness or a loss of particular qualities, such as response to temperature stimuli.

The reason why this is important is that to manage these kinds of conditions, we're going to have to rely on treatments that are actually disease modifying that will prevent progressive loss of sensory fibers, which will prevent terminal atrophy, and which may even promote regeneration of injured nerve fibers. At least in an experimental setting, there are interventions that we can now do, which do indeed prevent the development of neuropathy and certainly the negative symptoms.

And hopefully, this is going to be an area where further investment will contribute to additional approaches that can actually produce true disease-modifying therapy.

So this is not symptom suppression, which is analgesic. This truly is treatment that will be targeted at the actual damage that is occurring to the nervous system in response to different pathological cues.

Moving to positive symptoms, I'd like to now review several of the mechanisms that have been identified as drivers of pain in patients. And one of them is a change in temperature sensitivity. And this may occur as a result of changes in the actual sensitivity of peripheral terminals, which have particular proteins that have the capacity to transduce external stimuli into electrical activity.

The best examples of such a transducive protein is the TRP channel, TRPV1, also known as the capsaicin receptor. And this is an ion channel that is activated by heat and by protons and

endogenous opioid-like -- endogenous cannabinoid agonists. And when this channel is activated, it activates particular subsets of sensory fibers and generates the sensation of burning pain. And the reason why a chili pepper produces a burning sensation that is similar to the sensation that is evoked by an intense noxious heat stimulus is because both are mediated by this same channel.

Now, this channel's properties are such that its threshold is set, that it is activated at temperatures at the point in which a warm stimulus becomes injurious, which is around 42 degrees. But it can be modified. This channel can become sensitized, in consequence, that can be left with a shift in the temperature sensitivity, producing a heat hyperalgesia, an exaggerated sensitivity to heat stimuli.

So here is one feature of a patient's pain, exaggerated response to heat stimuli, which can be explained mechanistically by the involvement of the TRP channel and these particular sensory neurons.

Why is this important? Because once we

appreciate this mechanistically, that this is a mechanism that can drive this particular feature of pain, heightened heat pain sensitivity -- we have a mechanism, if you like. We have an element of the patient's phenotype, which is the fact that this patient's heat sensitivity has been altered such that their threshold falls. And now what we need to do is link the patient's phenotype, which is heat allodynia, with the mechanism as a driver of potential choices of therapy. And in this case, the therapy could be TRPV1 channel antagonists. It could be high-dose capsaicin cream, which desensitizes the channel.

This is the underlying thesis that I'm going to try and present to you, that if we identify the mechanism that contributes to the abnormal function of the nervous system, and can then pick up changes from the patient's own presentation, which reflect that mechanism, we can then make informed decisions about what are the best treatment options for that patient.

Here is another example. Here is

representation of an axon of a peripheral nerve fiber. And here we have several of the ion channels, the voltage gated ion channels, which contribute to the excitability of these axons. And these ion channels -- but particularly sodium channels, but also other cyclic AMP gated channels, the HCN channels -- are responsible for generating action potentials, but also for depolarizations, which can lead to spontaneous firing of action potentials.

Now normally, a sensory neuron is only activated by a peripheral stimulus. But if there is pathological excitability in the axon, then the threshold for activating action potentials can be reached. And this generates what we call ectopic action potentials. These are action potentials that arise not in response to a stimulus, but due to spontaneous changes in the level of depolarization of the axon. So this will generate -- because they'll get spontaneous membrane depolarization, firing of action potentials, which will produce pain-like,

spontaneous pain-like sensations in the patient.

Here is our neuropathology, which involves a number of ion channels, which can produce to this heightened state of excitability of injured axons. This generates spontaneous action potentials, which present in the patient as spontaneous bouts of pain. And once again, if we can link the patient's phenotype with the mechanism, we can then use this as a guide to the more effective targeting of treatment. And in this case, if the pathological excitability is a consequence of abnormal function of sodium channels, then the treatment of choice should be sodium channel blockers.

When we move to some of the changes that occur in the central nervous system, not surprisingly, the mechanisms get more complicated, but still they are important drivers of some of the aspects of the phenotype that patients with chronic neuropathic pain have. So if we look at what happens as a consequence of nerve injury, one of them is the general phenomenon of central sensitization, which is a change in the

excitability of neurons within the central nervous system, most particularly in the spinal cord, as a result of an increase in the strength of their synaptic connectivity.

The mechanism that drives this are multiple. But in essence, it could be summarized to saying there may be an increased release of transmitters and a heightened responsiveness of neurons, postsynaptic neurons, to these transmitters. And this increases the strength of the synaptic connections, which may amplify and exaggerate sensory signals. And this indeed seems to be one of the big drivers of many features of neuropathic pain. And in particular, it is the explanation for why activation of the sensory pathways that normally carry innocuous sensations can begin to drive pain. Because, normally, the fibers that carry information related to light touch do not generate pain. But when there's a heightened excitability or central sensitization within the nervous system, then what would normally be low threshold, or low-strength inputs, can now begin to

activate the pain pathway. And you can start to get a situation where light touch or stimuli that would normally evoke innocuous sensations now evoke pain. And this is an important feature of neuropathic pain.

So again, using the same argument, we have the neuropathology here, where we have central sensitization, such that input that would normally not drive the pain pathway begins to activate it, such as light touch. This presents in a patient as tactile allodynia, where lightly touching the skin now produces pain. And the question then is what is the best treatment for this patient, based on our understanding of this pathophysiology. And this should be to try and reduce either transmitter release or transmitter action. And there are drugs, such as the anticonvulsant pregabalin, which acts on the alpha 2 delta component of calcium channels and does reduce transmitter release.

So in this case, where patients have this presentation, the argument would be that these are patients who would most likely respond to this kind

of treatment more than if they had heat pain sensitivity, which would require TRPV1 channel antagonists.

A further element of neuropathic pain in patients is an alteration in the balance of excitation and inhibition. I've mentioned central sensitization, which is an increase in excitability that occurs in the nervous system of individuals after nerve damage. But increasingly, we recognize that another important component to the amplification of pain signals in the central nervous system is a reduction of some of the normal descending inhibitory mechanisms.

This is what we call disinhibitions. The normal inhibitory mechanisms that help suppress pain signals are lost. And in consequence, there's an amplification, there is a sensitization within the central nervous system, which contributes to a situation where the response to peripheral stimuli, whether they be innocuous or noxious, are exaggerated and prolonged.

Again, if we can identify patients where

there is a reduction in inhibition, then we can potentially do something about it. For example, dual-aiming uptake inhibitors, which promote the levels of both 5HT and norepinephrine, both of these act as part of the aminergic descending pathway from the brain stem to the spinal cord. And these drugs of this class can potentially reinforce this descending inhibition and help suppress the transmission of pain signals in the central nervous system.

From a pathophysiological point of view, one of the big advances has been our appreciation that there are not any major changes in injured peripheral sensory neurons and many changes in the spinal cord, but there are also changes in the brain itself. This has been relatively difficult to study preclinically, but fortunately, the advent of functional imaging has allowed us to begin to examine this in patients. And we'll be hearing something about this later on in the meeting.

But what this has revealed is that there appear to be both structural and functional changes

in the brains of patients who have chronic, persistent pain, to the extent that I think it's fair to say that the changes in the nervous systems of these patients is a disease state, and that we need to move away from an interpretation of pain as being only a symptom, to an appreciation that it is the maladaptive changes in the nervous system that is a disease of the nervous system that is responsible for the pain; and that we need to target our treatment at the prevention of these maladaptive changes and the suppression of them if they have already developed. This is an area that is relatively new, but there are many opportunities for future intervention.

So how to do this in practice. How can we identify the mechanisms that are present in our individual patients? We obviously can't take out their sensory neurons. We can't dissect out their spinal cord or access those parts of the cortex that actually drive the pain. So how can we actually do it?

Well, the answer is that we need indirect

measures. And the indirect measures we have are the actual disease phenotype. If we can measure the pain in our patients in a very sophisticated way, not just by asking them how bad is your pain from naught to 100 and where is it located, and some of its temporal characteristics, whether it's intermittent or continuous, which is really most of the standard questions -- but if we can ask much more sophisticated questions about the pain in our patients, we can get a window on the actual mechanisms that are operating in the nervous system of our patients. And from that we can get insight into what are likely to be greater treatment options.

So some of the kinds of measures we can take -- and I'm not sure you can read all of them here. But these are related to negative symptoms. So this would be hypoesthesia; reduced sensation to painful stimuli, to vibration; reduced sensitivity to thermal stimuli; spontaneous sensations; parasthesia; paroxysmal pain; pain that is superficial. And this list actually comes from the

German neuropathic pain network and Ralf Baron. And these are measurements that they routinely make in the large patient cohort they have collected.

Then we have positive symptoms, evoked pain. So these are spontaneous pains, and these are evoked pains. And these include mechanical dynamic allodynia, pain in response to the light touch; static allodynia; hyperalgesia, which is pain in response to a noxious stimulus; temporal summation of pain, et cetera. The point is that collectively, if measured in a systematic way in our patients, they can provide a fingerprint, a pain fingerprint, that may uniquely reflect what is going on in that patient's nervous system to generate the pain.

So here we have two patients who have been measured; all these features have been measured. And you can see how they differ. This particular patient has quite prominent negative symptoms. And this patient has spontaneous pain, whereas this patient doesn't. And this patient has a combination of evoked pain, whereas this patient

only has a small element of it.

So these patients, although both of them may have the same clinical diagnosis, such as postherpetic neuralgia, when examined in this way have quite different pain phenotypes. And this may reflect the fact that the mechanisms that operate in these patients are different.

So just to examine this in a little more detail, this is one of those two patients. And here we have a patient where their most prominent features are spontaneous pain. And if in this patient the spontaneous pain is arising as a result of abnormal properties of the sodium channels, then this would be a patient who would likely respond to a sodium channel blocker, as opposed to a blocker of alpha 2 delta subunits of calcium channels.

Here is another patient. And this reflects the fact that, unfortunately, the pain in our patients has not always been generated by single mechanisms. There may be multiple mechanisms that are present. So in this particular patient, there are prominent negative symptoms. And these may

reflect the presence in the patient of ongoing, degenerating changes in their peripheral nervous system. There are prominent stimulus-evoked pain, and this may reflect the presence of central sensitization.

This particular patient not only had central sensitization, but also had a reduction in their heat pain sensitivity. So this patient may require treatment that is targeted at TRPV1 at central sensitization, as well as treatment that can try and arrest the evolution of their external damage that's contributing to their negative symptoms.

So to sum up, I hope I've convinced you that in order to take a more rational approach to the management of patients with chronic, persistent pain, we need a more sophisticated approach to these patients. We need to get more information from these patients, information that will reflect what is going on in their nervous systems. This is not just for academic reasons to try and understand the neurobiological basis of the pain, but it is mainly an attempt to deal with the responder issue,

the point I made right at the beginning, that, at best, we only get a 25 percent response rate to any given treatment.

The fact that there is such a low responder rate means that if our treatment algorithm is empirical -- in other words, we have a patient with painful peripheral diabetic neuropathy, or postherpetic neuralgia, or HIV neuropathy, and we say to them, well, let's start you on treatment A, which may be duloxetine, or pregabalin, or whatever, and we'll see how you do, just based on the available literature, you'll need to treat four patients, as I mentioned, to get one who'll respond.

If instead of that, the empirical treatment algorithm, we try to develop a more rational approach to treatment, one that gives us insight into the underlying neuropathophysiology, we can then target the treatment more appropriately. And I hope I've convinced you that this individual neuropathology produces features in our patients, which can be detected, which constitute the

individual pain phenotype. And the combination of a careful history of the patient, careful examination as well as diagnostic test, give us the opportunity to define a patient phenotype that reflects the neuropathology, which can then result in a more targeted treatment of that pathology.

Thank you.

(Applause.)

DR. THOMAS: Thank you, Clifford. That was a very clear presentation of a very complex topic. And you might not know how complex it was because it was so clear.

Our next presenter is Roger Fillingim. He is a professor at the University of Florida, College of Dentistry, and director of the University of Florida Pain Research and Intervention Center of Excellence, and is the president of the American Pain Society, whose meeting last week was very nice.

Dr. Fillingim maintains an active research program, investigating individual differences in pain and responses to medication. He has received

numerous grants from the NIH and has published more than 150 articles and book chapters, and has edited three books and authored one. He has received numerous awards, including the University of Florida Research Foundation Professorship and the 2009 Wilbert Fordyce Clinical Investigator Award from the American Pain Society.

The title of his talk is Incorporating Quantitative Sensory Testing into Analgesic Outcome Studies.

Roger.

Presentation – Roger Fillingim

DR. FILLINGIM: Well, thank you, Dave, and thanks to Dr. Rappaport for the invitation to be here. And I do want to follow on Dr. Woolf's elegant presentation by talking about some of the examples of using quantitative sensory testing to do the type of mechanism-based phenotyping that Dr. Woolf referred to.

Here is a disclosure.

As we've already heard, a major problem is that pain diagnosis is based primarily on signs and

symptoms, sometimes combined with evidence of structural damage. But is not based on mechanisms, although mechanisms are what we treat. And so, Dr. Woolf is not new to this field. He and Mitchell Max, more than ten years ago, wrote a nice review on mechanism-based pain diagnosis, in which we depict that we usually try to identify the disease state or the injury, and that correlates to a syndrome.

We try to treat the syndrome, but what gets lost in the process is treating the mechanisms. The treatments target mechanisms, but we don't often measure these directly, and we don't know the mechanisms that are involved in many instances. Our treatment outcomes are based on measures of symptoms that are related to the mechanisms but are not complete proxies for those mechanisms.

So how do we do mechanism-based pain diagnosis? Well, there are some diagnostic tests. There are pharmacologic approaches. You can sometimes look at symptom clusters in patients to reflect pain mechanisms. What I'm going to be

talking about is the use of quantitative sensory testing for this purpose. You'll hear from Dr. Maixner about genetic markers, and from Dr. Mackey about brain imaging as additional approaches to mechanism-based pain diagnosis.

So what is quantitative sensory testing? It's the assessment of perceptual and/or physiological responses to systematically applied and quantifiable sensory stimuli for the purpose of characterizing somatosensory function or dysfunction. To put another way, in my hands, we hurt people, and we ask them how does it hurt. In one way or another, we obtain a sensory response.

We have a variety of methods at our disposal, electrical stimuli, contact heat, emergent heat and cold, mechanical stimuli, ischemic stimuli, and chemical stimuli to target many of the mechanisms we've just heard about. We also have a variety of measures that can be used, from simple measures like pain threshold intolerance to more complex processes, like temporal summation, conditioned pain modulation,

and on to physiological responses.

So quantitative sensory testing can become quite complex when we imagine all the combinations, but it's all intended to uncover pathology, mechanistic pathology, underlying a patient's pain complaints. And I've thought about several lines of evidence that have unfolded from quantitative sensory testing. And the first thing we might want to know is do patients or groups of patients differ in their QST responses from people not experiencing pain? And there are a variety of differences that could occur.

For example, here are some data from our recently published OPPERA study, comparing patients with chronic temporal mandibular disorders to pain-free controls. And you see a variety of pain measures here. We've got blunt mechanical pain or pressure pain here. You've got pricking mechanical cutaneous pain here. And then you've got a variety of heat pain stimuli in this box.

These are standardized odds ratios, such that any measure in which the 95 percent confidence

interval excludes one would be a statistically significantly difference between the two groups. So virtually all the measures are statistically significant, with patients showing greater sensitivity than pain-free controls, but you can see some patterns.

For example, blunt pressure looks like it generally has higher odds ratios than either cutaneous mechanical pain or than heat pain. If you were to think of regional differences, it looks like blunt pressure in the area of their painful complaint -- which makes sense. If you poke and prod them around the area where it normally hurts, they seem to be more sensitive relative to controls than when you poke and prod them elsewhere on their body. So we can see some differences potentially by stimulus modality and stimulus location in these types of data. Other pain conditions show similar patterns.

This is a study we did with QiQi Zhou and Nick Verne with patients who had irritable bowel syndrome. We measured ischemic pain sensitivity on

the arm. This is threshold intolerance. We measured cold pain sensitivity on the hand and foot, threshold on the hand and foot; tolerance on the hand and foot. Ischemic patients were generally more sensitive certainly to ischemic pain, which produces a deep, aching muscle pain. They were only significantly more sensitive than controls when tested on the foot, suggesting there may be some segmental aspect to their heightened pain sensitivity.

I mentioned earlier, there are more sophisticated measures. This is a measure of temporal summation by the group in Denmark. Temporal summation refers to a phenomenon in which repetitive stimuli, at the same stimulus intensity, become more painful with repetition due to a central nervous system adaptation mediated by activation of the NMDA receptor. So it's essentially a transient form of central sensitization.

Arendt-Nielsen's group tested osteoarthritis patients who had severe clinical pain and more mild

to moderate clinical pain. Overall, both groups showed greater temporal summation, both away groups, compared to healthy controls. And this is the increase in reported pain to a pressure stimulus as they kept getting poked repeatedly with the same intensity. And you see that particularly the arthritis patients with severe pain showed robust temporal summation of pressure pain, suggesting that this is a potentially sensitive quantitative sensory testing marker.

Some work we've done at the University of Florida examines endogenous pain modulation. As Dr. Woolf referred to, we all have these endogenous pain control systems, descending pain inhibitory systems that help us modulate our own pain. We can test this in the laboratory by determining the extent to which a pain stimulus at one site on the body inhibits how painful a stimulus on another site on the body is.

Here what you see in healthy controls, this is the painfulness of the heat stimulus applied to the hand. This is the painfulness of that same

heat stimulus applied to the hand when the opposite foot is immersed in painfully cold water. So that's a measure -- the difference between the open bar and the dark bar is a measure of pain inhibitory function. And you see the controls show a nice decrease in pain here. In contrast, patients with irritable bowel syndrome show no such decrease. And in fact, patients with temporal mandibular disorder showed a facilitation of pain rather than an inhibition of pain.

So we have several QST markers that distinguish patients from controls. Another question might be can we subgroup patients based on their responses to different pain tests or quantitative sensory tests.

These are actually healthy controls. Even in the healthy population, you can subgroup people. We have several different pain modalities represented here: ischemic pain, heat pain, pressure pain, and temporal summation of heat pain. We have one group of healthy individuals who were quite sensitive across all stimulus modalities. It

looks as if they were less sensitive to temporal summation, but that's only because there was a ceiling effect. They started out high and had nowhere to go. So they were sensitive across the board. But then we have other people who are particularly insensitive to pressure pain or are particularly sensitive to temporal summation.

So there are different profiles across pain modalities. A more clinically relevant example is from the very German neuropathic pain network that Dr. Woolf alluded to. They studied 1236 patients with a variety of neuropathic pain syndromes. And here you see the diagnoses represented, and here are their healthy subjects. And they have several different categories of findings. So some patients showed no sensory changes. Some patients showed only loss or negative signs. Some patients showed only gain or the positive signs. And then some patients showed a combination of both.

The important point here is, within a particular diagnosis, you see all subtypes represented. And so if these actually do reflect

different pain mechanisms, then a single pain treatment within the diagnosis is not going to do the trick. Similarly, if you look across pain diagnoses, you see commonalities. So some patients with polyneuropathy showed only gain. Some patients with trigeminal neuralgia showed only gain. And so these profiles may be better targets for treatment than the diagnoses themselves.

Another question we might address with QST is can QST before treatment predict how well patients might respond to treatment itself. Several years ago, the group at Johns Hopkins did a study. Rob Edwards was the lead author here. They had a clinical trial of both an opioid and an antidepressant. And it was a crossover trial in postherpetic neuralgia. The two medications were essentially equally effective, but they measured heat pain thresholds at a non-painful site before treatment.

What they show here is that the people who had a robust clinical pain response to the opioid had higher pain thresholds before treatment. So

their QST response, before treatment was ever initiated, predicted their response to the opioid. However, there was no association between QST responses and how well the antidepressant worked. So QST may predict responses to some treatments but not others.

A recent study by David Yanitsky's group in Israel, they looked at this condition pain modulation, that is the ability of one pain to inhibit another pain elsewhere on the body, and whether that predicted response to duloxetine in painful diabetic neuropathy. And in this study, what they showed is that those patients who had poorer inhibitory function before treatment actually responded more strongly to the treatment itself, suggesting that duloxetine may be targeting poor endogenous pain inhibition and can QST changes reflect the effects of treatment on the mechanisms we're interested in.

If we look at the same study by the Israeli group, we see that not only did baseline condition pain modulation predict treatment response, but

condition pain modulation got better. Lower is better for condition pain modulation, so that the more robust your clinical response to the drug, the more your ability to inhibit your own pain improved, again providing evidence that duloxetine may be targeting this mechanism.

Then the last study I want to highlight is actually a case report, which I think is intriguing and points toward future work. And this group from Germany performed QST in a patient with bilateral at-level pain following spinal cord injury. Pain on both sides was described the same way by the patient. It was burning, pricking, and severe in nature.

Here's a pain diagram of where the pain was. T9 was the at-level pain that they were targeting. It's probably difficult to read these graphs, but the bottom line is, on the right side, the QST findings showed normal sensation and cold hyperalgesia, suggesting central sensitization, as the authors interpreted. On the left side, there were primarily negative signs; that is loss of

thermal and mechanical sensation, or what they termed the "deafferentation." There was also greater epidermal nerve fiber loss on the left side; that is the deafferented side.

Pregabalin was provided as a treatment. It reduced the pain on the right, that is the central sensitization pain, but not the pain on the left. So this is a single case. We have to take that into account. But it's intriguing to imagine how this might apply to large groups of patients.

So in summary, before the red light comes on, quantitative sensory testing may facilitate mechanism-based pain diagnosis based on several patterns. One is that QST responses differ for patients versus controls. Patients can be subgrouped based on QST responses, which we believe might reflect underlying mechanisms. QST responses can predict treatment outcomes and can also reflect the effects of treatments on underlying mechanisms. And therefore, we believe additional research linking QST responses with mechanisms and treatment outcomes is needed.

And I thank you for your attention.

(Applause.)

DR. THOMAS: Thank you, Roger. I love it when the speakers watch the red light and care.

Our next speaker is Dr. Bill Maixner. He's the director of the Center -- he's at the University of North Carolina. He's the director of the Center for Neurosensory Disorders and co-director of the Pain Management Program. He also serves as a professor in the department of endodontics.

At UNC, Dr. Maixner lectures on topics related to pain mechanisms and pharmacology of analgesics. His major research interests are in the areas related to pain analgesia and pain genetics. He is active in such professional organizations as the Society for Neurosciences, the American Pain Society, the International Association for the Study of Pain, and the International Association for Dental Research.

He has published more than a hundred peer-reviewed papers. I think I'm on a couple of

them, Bill. And the title of his talk today is Genotyping as Biomarkers for Chronic Pain and Analgesic Efficacy.

Bill.

Presentation – William Maixner

DR. MAIXNER: Thank you, David.

Like the previous presenters, I want to thank the organizers for the very kind invitation to present today. In listening to the preamble to today's meeting, it's very clear that we're in a conundrum with the patient needs that are quite severe and substantial and some of the problems that we have in trying to deliver good care to patient that have resulted in some fundamental problems to society. And I think in large part, we should all recognize that we're here to improve the human condition, and that's what we are trying to do today I think.

What I'd like to do over the next few minutes is to speak about, really, a relatively new area as it relates to pain research and to the therapeutic treatment of pain conditions. I've

took liberty to change the title a bit from what David presented. I'm going to talk about genetic biomarkers as they relate to our ability to classify different patient populations. But we'll focus most of my time on talking about how we can use genetic biomarkers to identify putative new targets, both opioid and non-opioid targets, through which we think new novel therapies will emerge for the treatment of common, complex, persistent pain conditions.

Before going on, I would also like to note my disclosure. I'm a founder of a small biotech company called Algynomics.

Well, why do we care about biomarkers, whether they be phenotypic, such as we've heard about in the previous two talks, or genetics, genetic biomarkers? I think the thought is, the hope is, that by identifying biomarkers or potentially markers of risk pathways, risk determinants, risk factors, that these markers will enable better diagnoses and provide prognostic markers that enable and inform the clinician to

provide individual decisions regarding the potential efficacy and safety of not only pharmacotherapies, but behavioral interventions and invasive procedures that we use to treat persistent pain conditions.

It's also hoped that the identification of biomarkers will identify some of the underlying biology that underlies some of the mechanisms which were spoken of in the previous two presentations. And by understanding these mechanisms and the actual biological pathways that underlie these mechanisms, these traits, we will be able to identify druggable targets or targets that will be influenced by behavioral interventions as well. So I think there's a great need to develop and to identify novel biomarkers which will enable better treatment in the individualization of pain therapy.

Over the next few minutes, what I'd like to do is present two vignettes, where we have used human genetic associations to identify novel targets which we think will ultimately translate into novel therapies for patients suffering from

chronic pain.

Now, the assumption is that there is a genetic basis to a variety of common, complex, persistent pain conditions. And a review of the literature notes quite clearly that there's a strong heritability of most common, complex conditions, such as fibromyalgia, TMD, IBS, on and on. In fact, the heritability that's now been demonstrated across several different common conditions ranges from 30 to 50 percent, with a residual primarily related environmental influences on the organism.

Within the genome, there have been over the last, oh, ten years or so, several what we call candidate gene studies, where one looks for a relationship between genetic polymorphisms and the specific gene that codes for protein and its relationship to either a clinical condition or to the ability to predict drug response. And shown on this slide are several candidate genes which have been demonstrated -- some of them validated now in several cohort studies, which have been at least

putatively identified that are involved in certain pain conditions, such as TMD, lower back pain, migraine, on and on. And you can see this list is quite long and continues to grow.

So we've identified, at least from a theoretical perspective, a number of potential genetic and protein pathways that may lead to a variety of signs and symptoms associated with a number of complex, persistent pain conditions. And many of these genetic pathways may represent novel points of intervention for these conditions.

I'd just like to highlight that these genes and associated pathways really are associated with both the pharmacokinetic properties of certain compounds, like the opioids. So we have transporters which are involved in controlling these transport of agents like morphine into the central nervous system. There are genetic polymorphisms in the receptors, where opioids such as morphine interact, and the genetic variations in these receptors control the pharmacodynamic properties of the opioids.

So we have pathways involved in the pharmacokinetics as well as the pharmacodynamics, which have been demonstrated to influence the magnitude of response to agents like opioids. And I think we're going to see this over and over again with other classes of agents. But the point I make is that we now have evidence that there's a genetic basis to many pain conditions and that we have evidence that certain specific genes and associated pathways represent ways of identifying these patients for diagnosis, but also will help identify I think novel therapeutic targets.

I'd like now to begin to show you how we have used genetic association studies to identify targets and potential novel agents for the treatment of complex, persistent pain conditions. And I will show you in the context of what we call the translational research clock, where we start with human genetic association studies, where we identify a genetic polymorphism that relates to a specific condition.

The first vignette I'm going to show is a

genetic association study that came from a cohort of TMJD patients, patients which have chronic facial pain. And my colleague and I, Luda Diatchenko, identified a few years ago a polymorphism in a gene that codes for an enzyme, catecholamine o methyltransferase. This gene, an associated enzyme, has evolved in metabolizing stress catecholamines, like norepinephrine, epinephrine, as well as other catecholamines, such as dopamine.

So we early on showed that polymorphisms in the gene that codes for this enzyme was associated with an increased likelihood of developing a condition like TMD, and it was also associated -- these polymorphisms were also associated with the sensitivity to a variety of the noxious stimuli that Roger and Clifford mentioned earlier. So individuals who had certain polymorphisms and COMT were extremely pain sensitive and were at high risk for the development of TMD. This is one of the first genetic associations showing a relationship between a

genetic polymorphism and the risk of developing a chronic pain condition.

So this is part one on the clock. And the genetic polymorphisms that were identified by Luda and colleagues are shown here. We identified one variant of the gene, which had a group of alleles or SNPs that coded for high levels of COMT activity and were associated with very, very low sensitivity to pain. These individuals were pain resistant, and they were unlikely to develop conditions like TMD.

About 47 percent of the population that we studied had a haplotype that we called an average pain sensitive haplotype. And these individuals, when you looked at QST measures of experimental pain sensitivity, they showed an average sensitivity across several different modalities of nociceptor stimuli. And then about 10 percent of the population had a high pain sensitive haplotype. And these individuals were very, very sensitive to noxious stimuli and were much more likely to develop TMD than those individuals who carried

these other two types of genetic polymorphisms.

So we identified these genetic polymorphisms, but we then asked the question, is there any functional meaning to these associations. And then going to a proof of principle set of studies in in vivo and in vitro studies, we were able to show that indeed these polymorphisms, when expressed in certain cell lines, led to differences in protein expression, COMT expression, and did so through a rather novel mechanism, so that cell lines where we expressed the haplotype that codes for the low pain sensitivity genotypes showed high levels of COMT activity.

This is just a marker of COMT activity. So cell lines which expressed LPS haplotype were very, very robust in their ability to metabolize the catecholamines. This means that they expressed a lot of protein, which is also demonstrated by Western blots in this panel. In cell lines which had the average pain sensitive haplotype showed an intermediate level of COMT activity, and cell lines which expressed the high pain sensitive haplotype

showed very low levels of sensitivity.

So this clearly demonstrated that these genetic polymorphisms have functional effects on the enzyme of interest. And to shorten a bit this part of the translational clock, I would just note that the mechanism by which this occurred was through its effects on the tertiary and secondary structure of the messenger RNA such that certain SNPs in these haplotypes would permit the production of messenger RNA transcripts, which had different free energies for uncoiling, so they had different energy requirements for the translation of the transcripts into proteins. And this is one of the very first demonstrations by which genetic polymorphisms could alter protein expression by influencing the structure of the transcript.

We then went to conduct the in vivo study since we were able to show functionally that, in fact, these genetic polymorphisms were related to protein function. And we conducted a series of proof of principle studies in rodents, where we suppressed the activity of catecholamine o

methyltransferase, COMT, with pharmacological antagonists. And in so doing, we were able to kindle a human phenotype. So a group of rodents were treated with a pharmacological inhibitor of COMT, and then we assessed their pain sensitivity to a variety of stimuli, mechanical and thermal in nature.

What is shown here is that following COMT inhibition, these animals became very, very sensitive to mechanical stimuli. And if we look at the responses to heat, they became very responsive to heat stimuli applied to the hind paw. So these individual rodents began to take on a phenotype which mimicked the TMD types of phenotypes that we see in the clinic.

As Roger showed, these individuals in the clinic are very sensitive to mechanical and thermal heat. The suppression of COMT led to a phenotype which mimicked the human phenotype. And when we administered different types of pharmacological agents to try to rescue this phenotype, having gone through a whole series of receptor antagonists, to

alpha, beta, and dopamine receptors, we observed that agents, which when selectively blocked -- beta 2 and beta 3, adrenergic receptors -- would reverse this phenotype, rescue the phenotype, back to the normal sensitivity.

This data, this proof of principle, provided evidence that individuals who have a certain type of COMT haplotype, that they may be responsive to a non-selective beta antagonist, which then led to a proof-of-concept trial, which was conducted a couple of years ago and recently published by Inna Tchvialeva, where we showed in a group of 40 TMD patients, that were stratified by COMT haplotype, that we could predict response to the non-selective beta blocker propranolol, administered at relatively low doses in a double-blind, randomized crossover pilot study.

To show you these data briefly, 40 patients treated in a double-blind manner with propranolol, 20 milligrams BID. This is the patient preference as to whether they believed on the propranolol arm whether they had benefit. We see there is a

significant patient preference for the propranolol arm.

This is our measure of pain index, where we are multiplying the average pain over the day times the percentage of time during the waking day that the individuals are experiencing pain. If we aggregate the population where we're subtracting placebo from the propranolol treatment, we do see a significant effect on the pain index score.

If we stratify the individuals by their COMT haplotypes, individuals who had zero copies of this LPS, they have a very high catecholamine burden. They are much more responsive to propranolol than individuals with one copy or two copies of LPS. So individuals with two copies of LPS are chewing up the catecholamines quite well and are less responsive to the opioid.

It looks like we are very close to 15 minutes here. So I have finished one vignette for you, and what I would like to do, though, is just draw to you a conclusion, to draw to your attention a second very important area that's under

investigation now that relates to the mu opioid receptor. Using genetic association studies, we have identified a whole new splice variant, the mu opioid receptor that codes for an excitatory receptor, which is a druggable target. We have identified and developed in silico models and have screened over 2 million compounds, and have identified a number of putative agents which we believe will be very effective analgesics.

Confirming our early reports, Dr. Paternak, et al. recently published the functionality -- confirmed the functionality of this truncated isoform that we published on a few years ago, and identified a molecule which seems to produce high-level analgesia with little tolerance. Whether this new isoform will represent a potential new opioid target that is devoid of some of the side effects -- dependency, et cetera -- is still an unknown issue. But I will say that, again, using genetic association studies, we've been able to identify new targets, including opioid receptors that may represent very novel druggable targets for

the future.

Finally, I'd like to thank my colleagues from the Regional Center for Neurosensory Disorders and the many patients who have contributed to these studies. And I would like to say thank you very much.

(Applause.)

DR. THOMAS: Fifteen minutes goes real fast unless you're holding your breath.

Our final speaker in this section is Dr. Sean Mackey. Sean is the chief of the Division of Pain Management and associate professor in the Department of Anesthesia at Stanford University. Sean also serves as director of the Stanford SYSTEMS Neuroscience and Pain Lab. He is a member of the American Society of Anesthesiologists, American Pain Society, American Academy of Pain Medicine, and the International Association for the Study of Pain, among others. He sits on the Board of Editors of Pain Medicine and also Current Pain and Headache Reports. He holds two patents. He's the author of over 200 journal articles, book

chapters, abstracts and popular press pieces. And in addition to that, he lectures numerous times nationally and internationally.

The title of his talk is Neuroimaging Biomarkers for Pain.

Sean.

Presentation – Sean Mackey

DR. MACKEY: Thank you.

Thank you, Dr. Rappaport, for the invitation, also from the NIH. It's really a pleasure to be here. I have got 15 minutes to kind of bring this together and bring it up to the brain, where is the ultimate end organ for all of our experiences in pain. Before getting there, it's customary to give the disclosures. I have no industry conflicts. All of my conflicts are with the National Institutes of Health, which I'm trying to be more conflicted by them on a regular basis, as many of you are as well.

Many of you have seen these two first sound bytes, the hundred million Americans that are experiencing and suffering from chronic pain, half

a trillion dollar year problem. I want to drive home another sound byte that came out of the IOM report that I was on -- Dennis Turk and I think a couple of others here, who would be also happy to answer questions about the IOM report -- and that is that pain can become a disease in and of its own right, one that can fundamentally alter both the peripheral and the central nervous system, thereby setting up a state that is persistent and amplified.

Where this all started, this concept of pain, as we start this story now, all with Rene Descartes, who came up with this idea of dualism, this idea of the separation of mind, brain and body. And we were left with this 17th century philosopher model, up to the present time, where we've now gained a greater appreciation that in fact nociception, these electrical chemical events that occur in the presence of injury or trauma, is not equal to pain; that in actuality, nociception is really just part of the story, that it's not until it hits the brain that it becomes our

ultimate perception of pain, one that is modified, that's amplified, and modulated by a number of other factors: things such as cognitive factors, attention, distraction, catastrophizing.

This one here shows up probably as a more stronger implicator in how someone is going to experience pain and the persistence of it than anything else; contextual aspects, belief, placebo, whether patients are depressed or anxious. And then also, as was elegantly described, many of the genetic factors also play a role as well as early-life experiences.

We've spent the last decade or two trying to map out these regions of the brain that are involved with our perception of pain. We've identified a number of them, and they've labeled this term the "pain matrix" as a model to give this. And we're working hard to get away from that term because we're learning that many of these areas are not just involved with pain, but involved with many other perceptions: cognitions, beliefs, emotions. And not only that, but many of the

original areas identified in the pain matrix, in fact, that there are many more that are actually involved in that perception that are not included on that diagram.

You've heard from the other speakers this idea of individual differences in pain. And several of the speakers have very eloquently described what accounts for some of those individual differences.

This is a study that was done several years ago by Kim, et al. They gave a 49-degree Celsius stimulus; found that people reported it anywhere from zero out of 100, all the way up to 100 out of 100 and everything in between; identify that there are significant sex-related factors here, ethnic factors. Genetic factors play a role. But also anxiety, catastrophizing, somatization, personality characteristics also playing a role, which by the very nature defines this as a brain-related phenomenon.

Now Bob Coghill took this one step forward. And what he did is replicated that same exact study

with the 49-degree Celsius stimulus. He then broke people up into those who were high sensitivity, those who were low sensitivity, and found that the major areas of brain involved with those individual differences were related to areas such as the prefrontal cortical regions, the cingulate cortex, and the primary somatosensory cortex.

What I always think was very interesting in Bob's original study is that when you compare the high versus the low sensitivity, and you look specifically at the thalamus, you find that there is actually no difference between the high and the low sensitivity, suggesting that maybe we all transduce and conduct information in a very similar manner. But it's not until it hits above super thalamic regions that our individual differences start to be expressed. Now, that's one overly simplistic description of that, but it is a compelling finding and one that needs to be further replicated.

We've had a particular interest in this idea of emotional distress impacting our individual

differences. We've been intrigued by the role of fear and anxiety over the years; many, many studies showing that people who have increased fear and anxiety coming into an injury, more likely to have persistence of pain, more likely to have worsening outcomes with pain.

We took this and looked at it from an individual differences perspective, correlating the amount of fear of pain that subjects have to a specific stimulus, and find that, lo and behold, there are specific brain regions that seem to account for this. With regard to fear of pain, this right lateral orbital frontal cortex here comes up over and over again with a very high correlation with the fear of pain and brain activity; this region of the brain involved with evaluation of appetitive and hedonic and adversive stimuli in making decisions about what to do about those stimuli and those experiences.

So if we shift gears -- we've talked a little bit about some of the individual differences and how the brain can play a role in that. But

what about plasticity? What happens when pain goes bad and it fundamentally alters the central nervous system?

So one of the first studies that was done was by Vania Apkarian out of his group, in which he looked at patients with chronic low back pain. And this is not a brain activity study, but a structural study in which you use a standard T1 MRI to look at the changes in grey matter, comparing a group of patients with chronic low back pain and a group who are healthy controls. And what you find is that, by and large, we're all losing about a half percent of our grey matter per year after about the age of 30. Folks, that's the bad news. I keep trying to tell the people in my lab I'm learning how to use what I have left over more effectively. I don't think they're buying it.

But if you've got chronic low back pain, the numbers are about 5 and a half percent or so of premature grey matter loss, which works out to about a decade of grey matter loss as a consequence of just having chronic pain. And the majority of

those losses were found to be in these prefrontal cortical regions, regions of the brain involved with executive functioning, with working memory; it's keeping pieces of information in mind and manipulating it. And so maybe many of the patients that we see with cognitive dysfunction, we always attribute it to a mood disorder or the medications. Maybe it's due to the chronic pain itself.

So we can look at structure as a way of identifying plasticity within the brain, but are there other ways of doing this? And the answer is yes.

So there's a new very exciting way of looking at brain activity involving something called resting-state network analysis. And what we do here is, as opposed to the usual neuroimaging approaches in which we poke you or prod you with a stick, or a hot poker, or stick your foot in ice, here we just say, "Lie on the scanner for about 8 to 10 minutes and don't think about anything."

What happens is it turns out that while you're sitting there not doing any particular task,

there's a very slow alternating set of electrical activity, for the period of about 20 seconds, that connects a variety of different regions of your brain together. And so as you're sitting there not thinking of anything, as you're daydreaming -- and many of you may be doing that right now -- there is this slow strengthening connection between multiple regions of your brain. And that brain activity can be pulled out.

There are a number of different resting-state networks that have been identified, each with its own proposed function. One of those is called the default mode network. This default mode network, involved with self-referential thought, is thought to reflect maybe that little internal voice in your head. And so this study that came out a few years ago looked at the differences between healthy volunteers and those with painful diabetic neuropathy. And what they found is that there were alterations in this connectivity reflected in the default mode network in patients with neuropathic pain compared to

healthy volunteers.

Napadow and his group followed up with this -- looking at patients with fibromyalgia, a condition that afflicts 4 to 6 million Americans, 80 percent of them women, terrible, terrible pain. It takes a huge toll on their life -- and found that if you can compare them against healthy controls, what you find is in looking at networking, network connectivity of this default mode network with some of the sensorimotor areas, you find abnormal connectivity; that there are abnormal connections in these networks to other regions that are involved with bodily awareness and sensory function, showing, once again, that chronic pain is associated with fundamental alterations in the way information is flowing within our brain.

Now, the question I often get is, "Are these changes ultimately reversible?" I used to go out and talk about these grey matter changes, and it's a scary thought. People come away from this thinking, "Oh, my God. I have permanent brain changes. Can any of this be reversed?" And we're

starting to get some interesting information, and the news is looking good.

Now, this is a very complicated slide, so I'm just going to draw your attention to a few areas of it. And in this study that came out by David Seminowicz, who just won the Early Investigator prize at the American Pain Society, did a very elegant study with 18 patients with chronic low back pain. They did structural scans looking at grey matter, but they also did some functional scans investigating cognitive tasks.

What they did is they found that -- I want you just to focus on this particular one right here -- in patients with chronic low back pain, that there was thinning of the cortex around the dorsolateral prefrontal cortex. This is an area intimately involved with modulating pain and ultimately controlling and reducing it. These subjects all went through either spine surgery or facet joint injections as a treatment. They were scanned again. And what they noted was that there was a reversal of that dorsolateral prefrontal

thinning, and there was actual thickening of that.

At the same time, remember, they did these cognitive tasks, and they found that abnormality in these cognitive tasks and brain function in DLPFC. But then after treatment, there was a reversal of this brain activity, showing a nice correlation with treatment, improvement in the grey matter changes, and then also reversal of some of the cognitive effects associated with chronic pain, and also improvement in brain function in those same areas, giving us some nice hope that these effects are reversible.

What about opioids? This is part of the topic of this meeting today. Do opioids fundamentally alter the brain? And so we sought out to answer that question just recently. And here we're asking the question does putting people on short-term opioids fundamentally alter brain structure?

So we took patients with chronic low back pain who were on no opioids, opioid naive. Scanned them. Then ramped them up on long-acting opioids

for a period of time, a short period of time, about a month. We scanned them again. And what we found is that in fact there were fundamental changes in the architecture of the brain, in the grey matter, specifically in the right amygdala and some of the posterior cingulate regions of the hypothalamus and the pons. And the greater the dose of the opioids that they were placed on, the more the grey matter changes that resulted. We also followed them up about four months later after we took them off the opioids. And what was interesting there is that those changes had not yet reversed four months later. Now, we haven't gone out even further to see how long it takes for them to reverse.

So we're able to use neuroimaging now as a way of characterizing treatment, as characterizing improvement in patients' pain, and ultimately maybe leading to identifying biomarkers.

Speaking of biomarkers, as we bring this to some closure, I want to talk with you just very briefly about the next exciting direction I think we're going to be seeing in the area of

neuroimaging. And that's this area for using neuroimaging as an objective biomarker for pain. There's a clear need for this. We have current reliance on self-reported pain. It currently remains the gold standard. And I'll share with you as somebody who takes care of patients who suffer from chronic pain, I still rely a hundred percent on a patient's self-report. But there are clearly vulnerable populations where we would like to have a way of an objective biomarker, the very young, the very old, people in the ICU. We have a legal system that spends huge amounts of money trying to determine whether somebody is in pain or not.

Then the real reason we're all here today is we need objective biomarkers that we can use to identify mechanisms, mechanistic targets, as well as objective biomarkers that will help give us a sense of treatment responsiveness. Many efforts have been used to develop an objective biomarker: heart rate, heart rate variability, EEG, skin conduction, galvanic skin resistance. They've all failed miserably. And the question is, can we

ultimately use brain imaging to get us there.

So this may seem like we've already got this figured out, but the reality is, we haven't. Every brain imaging study to date in pain has followed this specific scenario. We take people and we cause them pain, or we take people and we know that they're in pain. And then we look at the brain patterns that occur as a result to that. What we haven't done up until now is to take a pattern of brain activity and then figure out is that person actually in pain, and how confident are we? How confident are we that they're in pain?

That's what we did with a particular study. It says actually in review. I need to update this because this was published just very recently. What we did is to use some machine learning approaches, the port vector machines, which are pattern classifiers. They allow us to place people in something called teacher space, that allows us to characterize whether they're actually in pain or not. Train the computer algorithm, and then put in novel data into that machine algorithm, and out

spits whether or not the algorithm thinks the person is in pain or not.

I was pretty skeptical about this when we first did it because I didn't think this could be done. We took 24 subjects, and we took 8 of them to train this computer algorithm on this basis of either getting thermal pain or just heat but no pain. Trained the algorithm, and then put in another 8 subjects to see how well it did. And lo and behold, we ended up with about 87 percent overall accuracy in determining whether or not somebody was in pain. I didn't believe it. So we ran another 8, and we got exactly the same results, with the secondary somatosensory cortex squeezing over into the posterior insula, the primary area that was discriminating this.

So this was all done under very carefully controlled conditions. But we're actually getting to the point where we can now discriminate whether somebody's in acute pain or not in acute pain. I want to take care to say that we're not saying that we can do this in chronic pain, not saying that

this technology applies to people who are trying to be deceptive or empathic of pain, but under very carefully controlled conditions.

So in closing things out, we're starting to see that neuroimaging of the brain is opening windows into the brain to allow us to peer inside to investigate causal mechanisms of pain, to understand the plasticity of pain, and to be able to look at treatment responsiveness of pain; ultimately, pulling together what previous speakers so eloquently described, pulling this all together into this model of personalized pain medicine, in this area of pain detection, which I promise you is going to be very, very hot in the next several years, we're going to be seeing more and more of this work trying to identify whether we can characterize pain versus other related conditions; whether there's commonality in distinctions, and then also to distinguish physical pain from imagine, from empathetic, from mood disorders, and also incorporating a number of multimodal imaging techniques, and then many of the techniques that

you heard earlier, such as quantitative sensory testing, genomics and other omic biomarkers.

I'll share with you one of my primary goals right now is to use this technology for good and to try to help avoid it being abused because there's been a number of other examples where this type of neuroimaging work has been used in improper ways.

I think we're closing right on time, and let me just give my thanks out to the folks in our lab, the Stanford Systems Neuroscience and Pain Lab, or SNAPL, where we study the best things on earth that hurt.

(Laughter.)

DR. MACKEY: And I'm thankful that the company let's me get away with that. Thank you all.

Questions and Answers

DR. THOMAS: Thank you, Sean.

I'd like to invite the speakers up for a short question and answer period before the break.

If you have any questions, please use the microphone and identify yourself and your

affiliation.

(Pause.)

DR. THOMAS: All right. I'll start. It's my job as moderator, and I like to ask questions.

So pain as a disease. Are we all in concurrence that it is a disease?

DR. MAIXNER: Yes.

(Laughter.)

DR. THOMAS: Okay. How about you.

DR. VON KORFF: Mike Von Korff from Seattle.

Sean, what do you make of these provocative preliminary findings on neuroplastic changes with short-term exposure to opioids that are sustained? I mean, what are the potential clinical implications of that finding?

DR. MACKEY: I think there were two questions there, what do I think about the neuroplastic changes, and I think you mentioned related to pain.

So when I show the structural changes related to pain, a couple things to point out. One is that we don't yet understand what those

structural changes represent. Do they represent changes in dendritic sprouting? Do they represent actual changes in neuronal cell density? Do they represent changes in fluid? Do they represent changes in glia?

Some of the work out of the depression literature suggests that it may be actual changes in glia, the supporting cells, that are causing this. Other work may suggest it's actually due to density of dendritic sprouting.

That's about all I know on pain. I don't know if my basic science colleagues would comment on that further.

With regard to the opioids, we're just starting to get a feel for the changes that opioids cause in the brain. I'll share with you that a decade ago, I would tell my patients that there was no organic toxicity related to the use of opioids. I don't say that anymore. I appreciate now that opioids do fundamentally alter the brain. We don't know yet the ramifications of that and to what extent or what period of time it's reversible.

DR. MAIXNER: I just want to go back to Dave's question. We all gave a glib yes to that question, but I think it's a very important question, and there are a lot of nuances to that question. I think one of the primary nuances is when does pain becomes a disease, what are the features that cause a trigger from acute pain, which one recovers from well and where the nervous system shows rapid recovery from the sensitized state back to a normal state back to a normal state? What are the triggers that diminish that capacity to come back to a normal phenotype?

That's very critical for us to understand in order to understand the disease process. And then to truly relate this to a disease is to try and understand these switches that lead from acute to chronic pain. And I think that we are in that process now. I think that we've reviewed some work that's occurring in the German pain network, work that Roger Fillingim and I are doing in a larger program called OPPERA. We are seeking to identify those signatures, those pain signatures that an

individual carries prior to a pain state to determine if we can identify those biomarkers, risk factors, whether they be phenotypic or molecular in nature, that put one at risk for the development of a disease such as chronic pain.

So it's a very important question actually, David. And I think it's very important for us to understand that switch in order to both intervene from a prevention perspective, but then also to understand how we treat these subpopulations of patients that we identify by molecular profiling and by clustering phenotypically.

DR. WOOLF: I think we were too glib in the sense of saying pain is a disease because it is a disease in some situations. Pain ultimately is a warning system. It informs us of the presence of damage, and without that, we would end up in big trouble because we were not aware of either environmental damage or a disease state of our internal organs.

I think that's a warning also in terms of our treatment. Our treatment needs to suppress

pain but not switch it off because we lose that warning system. So there are some pains where pain is adaptive. And I think if we have a damaged joint, for example, this becomes more complicated because the pain may be persistent, and yet the damage to the joint is persistent. And is that pain a disease? I'm not so sure it is. And there are concerns with the new anti-NGF treatment, that it may almost be too effective such that patients are now overusing joints that are damaging, putting at risk the need for earlier joint replacement.

So I think there are clearly some states where the adaptive function of the pain system has been completely lost, that pain arises spontaneously. It no longer serves any useful adaptive function. And those extreme cases are definitely a disease state. And in particular, those cases where there is demonstrable abnormal function of the nervous system, there is another element where pain can be persistent but still have its adaptive, protective role.

DR. MAIXNER: And just one other comment,

given the topic of today relates to opioids and the effects of opioids and pain treatment. I think that it's becoming clear that these different isoforms or mu receptor proteins vary greatly in the population. And there are certain variants, these truncated variants, which I didn't have a minute to speak about -- but these truncated variants are associated with great enhanced pain sensitivity.

Individuals who carry this type of variant are resistant to the effects of morphine. And so it would suggest that these variants, individuals who carry these variants may be at risk for chronic pain conditions. They may be less able to obtain an efficacious response to opioids. And they may be at risk -- given where we've shown the expression patterns of the isoforms, they may be at risk of dependency and tolerance to opioids.

So I think we're coming up with some new biomarkers that relate to the prominence of opioid pathways in susceptibility for chronic pain and that also predict morphine response acutely and may

actually predict susceptibility to morphine's side effects with chronic use. So I think there's a whole new biology that's beginning to emerge now in the opioids biology.

MR. ALI: Syed Ali from Pfizer. Question for Clifford Woolf.

Is it reasonable to say that the great work that's been done by the German pain network really represents just one snapshot in time of the patient's sensory profile? And the second component of that, do you think it's reasonable to also think that there's some degree of potential oversimplification in terms of trying to classify patients based upon their sensory profile in terms of their treatment? Because a patient who's in spontaneous pain may also have sensitization over time, may also have plastic changes in the central nervous system, thereby representing multiple changes within the normal physiological pain system, leading to complex pathophysiology, which may mean that the treatment itself may be complex in providing relief for that patient.

DR. WOOLF: Yes, I think you've really hit the nail on the head, which is, our understanding of the patient disease phenotype, at least when examined in detail by quantitative sensory testing by imaging, is usually one snapshot. And often the patients are on therapy, so we have very limited data on the dynamic changes that occur over time. There is certainly enough data to suggest that it is plastic and does change. And therefore, when I use the analogy of a pain fingerprint, it's likely to be very macular because our fingerprints do not change. And yet it is very likely that the pain phenotype has a dynamic component that will reflect the natural history of the disease, the genomic influences and the response to treatment.

So we're just at the beginning of this. I think we need to develop the tools to address this, to accumulate the large patient cohorts that are required to give us very clean answers. There are some very interesting data, twin studies for example, that are revealing which of those elements are likely to be heritable and which are more

influenced by the environment. But I think we have begun to ask the right questions, even though we don't have all the answers yet.

MALE SPEAKER: Question directed at Drs. Woolf and Mackey. Could you comment on the role of inflammation -- a word which really wasn't mentioned during the four presentations -- both on the pathophysiology of the different types of pain that you've described in the initial talk, and then in terms of the changes in imaging, especially functional imaging, that would accompany chronic pain associated with inflammation.

DR. WOOLF: Just a brief response. I think to me, increasingly -- I just mentioned the adaptive function of pain as a detection of danger within a central protective role. And that's exactly what the immune system has as well. The innate immune system and the nociceptor system, if you think about it, are both designed to respond to danger, to elicit a series of responses to deal with that danger.

We've tended to study them independently,

but in fact they act together. And, unfortunately, not only do they act together in an adaptive function in many cases where the sensitization that the immune system produces, and the pain system to produce inflammatory pain, is an appropriate adaptive function, but they also maladapt. And the interaction between the two systems clearly is at least a driver, in some cases, of chronic, persistent pain.

That is true both in the peripheral -- in conditions where there is clearly a detectable immune component to persistent pain, such as in the arthritides, but increasingly we realize that neuropathic pain has a very large immune component. Damaged nerves have many macrophages, T cells and neutrophils. These talk to the neurons. The neurons talk to the immune cells. And then within the central nervous system, the microglia, which are the resident macrophage-like cells within the nervous system, are massively activated after nerve injury and are part of the means by which the permanent changes occur.

There have been attempts to look at activation of microglia in humans. And there are some studies mainly geared to MS-like conditions. But it would be wonderful if we had the resolution to separate neurons, glia, and microglia in human patients.

DR. MACKEY: I think Clifford really nicely described the problem we have in trying to separate the effects of pain, the effects of the immune system and the inflammatory system, whether it be the peripheral, the central nervous system. And to date, we don't have a way of really teasing those apart.

There are some PET ligands that have been developed, I think a peripheral benzodiazepine receptor that have been used to monitor glial activity. Not many studies have been done with it yet. It is starting to get out there more, and we're developing more advanced techniques to be able to look specifically at the inflammatory component, but right now we can't really tease those apart in the CNS at a human level.

DR. THOMAS: Okay. We have time for one more short question.

DR. SINGH: Jasvinder Singh, University of Alabama. The functional MRI images were very nice, but my question is, typically the biomarker is used either as a diagnostic pain/no pain; prognostic pain leading to a lot of disability/not leading to a lot of disability; or predicting response to therapy A versus B.

How do the data, currently as it exists, help us in doing that? And does functional MRI as a biomarker meet the criteria of being more visible and/or telling us something more early in the disease than the symptom of pain?

DR. MACKEY: More broadly, I don't think we're yet ready to use functional MRI or any of the techniques that I mentioned in a clinical environment to help us guide decision making to guide therapy. We're not there yet.

We recognize that many of the studies that I showed you are showing correlation, not causation. So we haven't been able to get down to the level of

detail to show specific mechanisms. We're staring to see more sophisticated designs in functional imaging that will allow us to do mediation analysis and really get at the sense of what is causing what.

I think it's pointing us right now to targets that are exciting to go after, whether those targets be mind/body therapies, psychological therapies, or drug targets. And I think the sophistication of the studies is improving greatly. And I think there's tremendous promise for the future, particularly with I think some of the technology I was showing at the end that now many investigators are getting into with these multivariate pattern classification techniques. I think it's still going to be a while before we get to this being used in clinical decision making.

DR. THOMAS: Thank you, Sean.

This concludes the initial session. We're going to take a 15-minute break. Thank you. There's a snack bar -- I believe it's open -- right next to the cafeteria. And if you'd please join me

in thanking our speakers.

(Applause.)

(Whereupon, a recess was taken.)

DR. THROCKMORTON: While people are finding their seats, I'm going to go ahead and get started and introduce the next session, which is going to be somewhat of a change from the things that we've talked about up to now. Rather than the science of pain, we're going to start transitioning now toward an understanding of the nature of the epidemiology of pain, understanding better the clinical uses and misuses of the pain medicines that we're here to discuss today and tomorrow.

By way of introduction, I'm Doug Throckmorton. I'm the deputy center director at CDER, and I'm the co-moderator of the overall meeting. It's my distinct pleasure, though, to introduce Dr. Len Paulozzi, who's going to be moderating this next session.

Len has really done tremendous work over the last almost 20 years now, I understand, at the Centers for Disease Control and Prevention, working

on the epidemiologies of injury in a variety of settings. But I would say my particular encounters with him have been particularly around the epidemiology of injury due to inadvertent use of prescription drugs, including prescription opioids. And in that setting, he's done seminal work in a variety of ways.

Len, I look forward to the session this afternoon. Thank you very much.

(Applause.)

Moderator – Len Paulozzi

DR. PAULOZZI: Good afternoon, everyone. We have a lot more in the day today, and I've been told to try to keep this on time so that we can get everything in today. So I'll be brief.

I'm a medical epidemiologist, as Doug was saying, at CDC's injury center. And I've done work on the adverse events of prescription drug abuse and misuse; in particular, prescription drug overdoses. As part of our role as an injury center, our mission is to prevent injuries such as overdoses, which are a type of poisoning.

So our focus has been on safety rather than effectiveness. But yet, effectiveness is particularly important when it comes to policy discussion, when we are trying to balance the costs of treatment with opioid analgesics for pain and the benefits. So I think this is an important conference in terms of addressing the balance between what we may know about the costs and what we still need to learn about the benefits of opioid use for chronic pain.

This session deals with the epidemiology. It's going to be descriptions of populations. We're first going to hear about the epidemiology of chronic pain, and then about the epidemiology of the use of opioid analgesics to treat chronic pain.

We're fortunate to have two very distinguished speakers on this topic. The first talk is going to be by Dr. Walter "Buzz" Stewart, who is an epidemiologist, and therefore near and dear to my heart. He got his Ph.D. in epidemiology at Johns Hopkins University. He was on the faculty at Johns Hopkins School of Public Health for a

dozen years. In the mid '90s, he became involved in private research companies.

In 2003, he started the Geisinger Center for Health Research, with a focus on novel approaches to health care. And he is now the associate chief research officer for the Geisinger health system, located in Danville, Pennsylvania. And his talk is the Epidemiology of Chronic Pain in the United States.

Dr. Stewart.

Presentation – Walter Stewart

DR. STEWART: Thank you, Len. It's a real pleasure to be here. Len told me to see if I could catch up and close the gap on time, so I'm going to say I'm done. Are there any questions?

(Laughter.)

DR. STEWART: Not really. I'm not going to be that generous.

These are my disclosures. I do both analysis of longitudinal electronic health record data and in-practice trials around pain management. I'm going to focus on chronic pain epidemiology,

and not just confined to the U.S. but sort of worldwide, and probably mostly the western part of the world.

It's hard to talk about chronic pain, in particular, the class of disorders that I'm going to focus on, which are the nociceptive pain disorders, which make up most of the pain that you see in a healthcare system. I refer to these as chronic pain disorders with episodic manifestations. And I use this framing because I view them as part of a broader family of disorders that have this sort of same epidemiology. They're conditions that people have for varying periods of time, from a year to many years, perhaps a lifetime. And other conditions that are part of this family are conditions like asthma, GERD. There are a whole set of conditions that are part of our frailties that can evolve into a condition that's more severe, but often they remit.

I want to build on some things that were said earlier about pain as a disease. And I view pain as really a chronic progressive disease, where

most individuals remit, but individuals do progress through stages to a chronic, persistent pain state. And in many ways, I think there are analogies between what we can observe and what somebody experiences with their pain condition, and what happens episodically, and what we might think happens with a disease like atherosclerosis, where there are insults to the endothelium and other parts of the vascular system that accumulate over time. Sometimes they remit to a normal state, but often they can progress to a more severe state. And in many ways, I think pain has a similar kind of framing. So I'm going to come back to that.

I think of pain conditions like migraine and low back pain in the same way that I do think about chronic progressive diseases. And so I bring in the same sort of concepts that I think we have to think about, the notion of prevalence, which is the number of active cases in the population over the population. And prevalence is the product of incidence, new cases coming in, and remission, cases moving out. And it turns out that for many

of the common pain disorders, the remission rate is fairly high. So a normal adaptive response is something that is the most common.

If you look at migraine, where the cumulative incidence, lifetime incidence, of migraine in women is 48 percent, and the standing prevalence is 17 percent. Most women remit, and so they have an adaptive response that is normal. And we tend not to sample from those who do adapt well.

A lot of what we saw in the earlier session was what I would consider to be more the end stage of the disease without having a full understanding of the spectrum of those who move in and out of various stages. And I think we have to be conscious of that as we think about the common pain disorders.

So just a quick flyover of what we know with regard to the epidemiology of the common recurrent pain disorders. They are the dominant pain disorders in the population. They're very common. It's not to exclude of course neuropathic pain, which is severe and tends to be chronic persistent,

and then other pain that arises from diseases or events.

The point has been made earlier today that the source of most of our data, if not all of it, is self-report. I don't believe that there's any way that we can get away from self-report. I think we can do a much better job of improving how we measure it, but I think that when you think about eventually bringing things to clinical practice, it's going to have to be based on self-report. The question is, can we design better instruments, using biomarkers, using imaging markers, as a way to validate how we measure what people tell us and knowing when what they're telling us is an error or credible and valid.

You saw some cost data. There are two major categories of costs, direct medical costs and what is characterized as indirect costs. I think whether it's an indirect cost depends on who you are. If you're an employer, it feels fairly direct. But a significant share of the overall cost of the common pain disorders is really a

work-related cost, and I'll come back to that.

Then I just want to make one other sort of key point, which is, in contrast to many other areas of epidemiology, our knowledge of the epidemiology of pain disorders is relatively primitive. We have a lot of cross-sectional studies where we're looking at prevalence, but we have a fairly primitive understanding of how individuals come into the prevalent pool and leave it or progress. And it's really remarkable when you think about how common the pain disorders are that we suffer from, the enormous impact, and yet how little we know in terms of the dynamic life course of this condition.

So how common is chronic pain? This is a summary right here of the prevalence of chronic pain across many different studies. The one in the middle is WHO Mental Health Survey data from many different countries. But if I asked you do you suffer from chronic pain, many of you might raise your hand and say yes. And then as a fundamental question, did you understand what I meant, did I

understand what I meant, and are we really measuring it accurately.

So this is one of the challenges. How do we measure chronic pain? I could ask you if you suffer from chronic pain. I could delve into the details of your pain experience, and then separately define you as suffering from chronic pain, which is the preferred method. But this has to be an important and intensive area of study for the future, in terms of coming up with credible and valid ways of measuring pain in the population because so much of what we can advocate for I think depends on the credibility of our measures.

So if you look at just general chronic pain, there's a 2.8-fold variation in prevalence estimates across studies. If you even take a narrow range, it's 1.7. I would say this picture probably is not credible with regard to how we think of chronic pain.

You can think of refining the definition to something that perhaps has a more observable component, both the pain experience that somebody

reports that may have a subjective component and the impact that that has on them. And the prevalence is lower and the range is a little narrower adding more credibility.

So we have to think about what we mean by chronic pain. Certainly as we move to the right on this curve, where we're thinking about chronic disabling pain, the prevalence and the variance across studies goes down. But even chronic disabling pain has a prevalence in the general population of 10 percent, almost 10 percent. It's extraordinary to think that it's that common in the population.

This slide just shows the prevalence of active pain in a number of different locations, from head to toe. And the prevalence does vary substantially, depending upon the location. And the duration of time actually that somebody has had it for three months or more is more consistent across these pain sites.

Not surprisingly, the proportion of those who have the pain disorder, who have had pain

episodes on the half the days or more, which we would characterize as chronic pain, varies substantially from head to toe. And not surprisingly, it's higher in the toe than it is in the head because it's probably more gravitational force irritating and causing persistent pain in lower limbs than in the head.

Then if you look at the impact, the overall impact really is a product of the proportion who have the pain condition of the population and the proportion of those who are functionally impaired. And of course that varies substantially, but you have to consider the original denominator to understand the overall full impact of disease.

So time doesn't allow me to go into depth into defining who gets the pain, but I'm just going to cover with a quick flyover some of the features of the populations that are at risk. So you've heard earlier that certainly females tend to be at higher risk, although it's not universal for all pain conditions. I'll come back to that.

With regard to age, it really varies

substantially depending upon the pain condition that you're talking about. So migraine has a median age of onset in the early 20s, whereas low back pain is in the 30s. Arthritis is later. So all of those various conditions have a very different age profile.

What they all have in common is an income and education gradient. So if you look in particular in the U.S., we see that the prevalence of all of the pain disorders are inversely related to education and income. And if you look at these conditions in European countries, the gradient tends not to be as strong. Take migraine for example, a fairly strong gradient inversely related to income in the U.S., but almost the absence of it in European countries. With regard to race and ethnicity, especially if you adjust for socioeconomic status, prevalence of pain disorders tend to be lower in Asian populations, higher in Caucasian populations.

Then interestingly, when you look at the general population, the co-occurrence of these pain

disorders is common. And as somebody's individual pain condition gets more severe as they progress, they acquire co-occurring pain in other sites and locations. So these tend to migrate together.

The risk factors that are related to having persistent pain, I would say they're the usual suspects. But some of these, like BMI, may play different roles. So BMI may play a physical role for something like low back pain or lower joint pains, but for a condition like migraine, where we know that the frequency of migraine attacks is associated with higher BMI, it may be that BMI is playing an inflammatory mediating role.

So let me just drill down a little bit for each of these factors. It's well recognized that females are more likely to have some pain disorders, not all. And I think an interesting area for study is to understand factors that mediate risk of pain disorders where there's a female preponderance for something like migraine and where there is not. This gender pattern is consistent across cultures and time, and I think

it's an area that I would say is understudied and where there's probably enormous opportunities for us to learn etiologic clues.

I mentioned that pain varies both in incidence and prevalence by age. This graph shows four different pain disorders and the impact on work function for migraine as a younger age of onset. So we see in the workforce that the impact is predominantly at a young age, whereas back pain, which is shown here, is sort of more broadly across all age groups. And then you have the more progressive disorders, arthritis and general musculoskeletal pain increasing with age.

The episodic versus chronic variance of these common pain disorders also differ by age. In this graph, I show the age-specific prevalence of migraine for females in purple and males in blue. This is the episodic variant, but if you look at the chronic daily headache variant, it has a very different shape, suggesting that at least at a younger age, perhaps there's susceptibility and transitioning to chronicity, as well as a mode that

reflects the peak prevalence of migraine. So something may be going on that mediates the transition to this chronic state at a young age and perhaps progresses later on. The shape of this curve for females is very, very different than it is for males; again, suggesting differential susceptibility to chronicity.

I mentioned earlier that migraine and other pain disorders are inversely related to socioeconomic status. On this axis here is the prevalence ratio, where the lowest income group is 1 and the others are relative to that. And you see the same gradient. This is for migraine, the prevalence ratio of migraine in relation to income, and a very sort of strong relationship.

You see the same thing for back pain. In this case, education is used as the SES gradient. This to me is a fascinating contrast between the prevalence of osteoarthritis of the knee based on radiographic imaging versus pain experience actually reported in surveys, and very, very different patterns, suggesting of course that

factors in the -- this is in relation, I'm sorry, to education, years of education; that there are factors that mediate this experience into something very, very different in terms of how people experience the underlying pathology.

This is for females. This is for males; again, a very, very different epidemiology. The radiographic epidemiology is in contrast to that for females, perhaps related to occupation. And we don't see the same kind of gradient in terms of how education level translates into pain experience.

When you think about the variation in prevalence by income and education, in that inverse relationship, there are always three major classes of explanations that come up. So one is what's called downward drift. And so if you have a condition that impairs function, especially early in life, and your ability to work, then what can happen over time is that you drift downward economically into a lower income bracket. And the effect of that is to increase the prevalence in lower income groups and decrease the prevalence in

higher income groups.

A second category of causes is what is called social causation, influencing the actual onset of the disease. So there may be social -- or stressors in the social milieu that put you at higher risk of having an incident onset. And then there could be social factors that lead to persistence of disease over time or a lower remission rate over time.

So these are always the three categories of causal explanations that arise. And I'm just going to share with you some of our own work that Richard Lipton and I have done on looking at incidence in remission of migraine. So if you looked at social causation as the explanation, we'd expect the incidence gradient to be inversely related to income. If you looked at social causation and its impact on persistence, we'd expect that the remission rate would be lower for lower income groups. And then downward drift would say nothing about either the incidence or remission rate.

In this graph, I show the inverse

relationship between migraine prevalence, age-specific migraine prevalence, in females and income. So you have low income, middle income, and higher income. And you see the same gradient for males. And if you look at the incidence rate, you see that the onset, age-specific onset, mirrors what we see here in prevalence. So the inlet pool is being fed to create this gradient because the remission rates actually are not different by income level.

So these data suggests that SES, the way that SES -- and actually, the influencing, the gradient that we see in prevalence, by increasing the incidence, but the remission rate pretty much stays the same. And I think that that has perhaps a fundamental impact in our thinking about how does disease drive through a population a pain condition like migraine, or all the others that have this same sort of prevalent gradient. And that it may be that it's the onset of the pain experience that triggers. And once somebody gets it, they're committed to the natural course of that disease,

whether it remits or translates into a progressive disorder.

I'll just close with a couple of other comments. One is on functional impact, a lot of focus on the work impact of pain because it's such a common condition in the workforce. There are always two important ways to think about it with regard to who pays other than the patient. So the employer pays substantially when there's work absence or reduced performance. Society pays when somebody transitions to unemployment. When you look at health problems in the workforce, pain is by far and away the most prevalent condition in the workforce, by far, and it's the most impactful. And so it is a condition that employers should be concerned about.

If you look among those who are employed and the most common pain disorders, the most common episodic pain disorders, they account for more than $60 billion in overall costs. But this represents only a share of the overall costs because we know that as the frequency of episodes of pain goes up,

the risk of underemployment and employment also go up, directly.

This slide here, the same study that we did a number of years ago, just shows the proportion of those each week who lose at least two hours of time by pain disorder. Headache is dominant here because headache is so common in the population. And so you have to think about that background prevalence I think to interpret these data.

I'm just going to close with a few comments about the co-occurrence of pain conditions. This is the prevalence of individuals who have at least one of five different pain conditions. You can see early on in life, in earlier decades of life, that there's a female preponderance, and that that narrows as individual's age. But the picture is dramatically different when we look at the proportion of those in the population who have three or more pain conditions, that the separation between men and women is profoundly different.

When I think of -- I live in a healthcare system. I run a research center within a

healthcare system, and I think about what goes on in primary and specialty care and what happens day to day when people come in for care. And most of health care is organized to diagnose and treat single pain disorders, especially in primary care. We don't think of treating multiple symptoms of pain, yet many people in the population who suffer most have multiple pain disorders.

When I think about the pain as a chronic progressive disorder, if you look at individual pain conditions, people are beginning to think and evolve chronic pain models, but we don't have a universal chronic pain model that helps us think through how the pain begins, how individuals accumulate multiple pain disorders, and what the end stage disease looks like.

So I'll stop there.

(Applause.)

DR. PAULOZZI: Thank you, Dr. Stewart.

Our next speaker is Dr. Michael Von Korff. Dr. Von Korff is a senior investigator at the Group Health Research Institute, Group Health

Cooperative, located in sunny Seattle. His research concerns deal with management and outcomes of chronic pain, depression, and other common chronic conditions among primary care patients. He has led work on large randomized control trials of healthcare innovations, including collaborative care programs for depressive illness and self-management programs for chronic recurrent back pain. His current research concerns use of opioid medications for chronic pain and associated health effects, prognostic models for chronic pain, evaluation of collaborative care models, and more.

Dr. Von Korff.

Presentation – Michael Von Korff

DR. VON KORFF: Thanks a lot, Len.

It's really great to be here and see old friends and acquaintances and to meet some people I've known by reputation but never had the chance to meet.

I was asked to talk about the epidemiology, what epidemiology has to say, epidemiologic data on long-term use of analgesics in general and

long-term chronic opioid therapy in particular.

There are two things that I think epidemiology brings to this. The one is thinking of this problem in terms of the community-wide perspective. Does a treatment regimen work the way you think it's going to when you take it from say a specialty clinic out into the general population and are doing community-based treatment with very heterogeneous patients and very large patient populations? The second issue is, what's the balance between benefits and risks? So when an epidemiologist thinks about effectiveness, both benefits and risks are in play.

I have some of these NIH competing interests, too, the National Institutes on Drug Abuse; and on aging of supportive -- my opioid related research. I have research on back pain supported by pharmaceutical companies.

In the year 2000, 2 to 3 percent of U.S. adults were using opioids, NSAIDs, or acetaminophen on a regular basis for a month or more. This amounts to about 4 to 6 million people using each

class of these medicines. When you have large numbers of people being exposed to drugs like these, it means that it's essential to understand how they're used and what their effectiveness and safety profile is in community-practice settings with the patients that are getting them by the providers that are actually prescribing the drugs.

Females and older persons are more likely to be long-term users of analgesics. As Buzz just told you, they have a higher prevalence of chronic pain that increases with age. It's higher among females. So this mirrors that. Persons with lower levels of education and non-Hispanic Caucasians are also more likely to be long-term users of analgesics.

Over the past two decades, there's been a marked increase, a dramatic increase, in the use of prescription opioids in the U.S. population for every specific drug except codeine. Health plan data has also shown that there was a doubling of the prevalence of the adult population using chronic opioid therapy, using opioids long term

between 1995 and 2005. More recent drug enforcement data has shown the per capita retail sales of opioids have continued to increase through 2010.

This increased use of opioids for chronic pain has some very important implications. It means that more patients are using opioids for months and years rather than days or weeks; that more patients are using opioids at higher dosage levels. And it also means that the increased availability in our communities of opioids for non-medical use is increased. So understanding the public health implications of these changes and how opioids are being used has largely come through morbidity and mortality surveillance systems.

Analyses of U.S. mortality data by Len Paulozzi's group at CDC has shown that the rate of fatal drug overdose involving prescription opioids increased fourfold from 1999 through 2009. Analyses of drug treatment data by the Substance Abuse and Mental Health Service Administration has shown that the admission rate for treatment of

prescription opioid addiction also increased fourfold from 1999 to 2009.

It's unusual to detect adverse health effects of prescription drug changes and prescribing of prescription drugs with national surveillance data. So as Bob Rappaport indicated at the beginning of this meeting, this is something that needs to be taken very seriously. Understanding these trends from aggregate ecological data requires more refined analyses directly relating drug exposures to potential adverse outcomes.

Recent epidemiologic studies have found that chronic opioid therapy patients receiving an average daily dose of 50 milligrams morphine equivalents or greater increase risk of prescription opioid overdose relative to patients on lower doses. To be clear, this research relates average daily dose dispensed to overdose risk, not the opioid dose consumed immediately prior to drug overdose. These studies, published in the last couple of years, were the first to directly link

exposure to medically prescribed opioids, with drug overdose risks among patients using opioids for chronic pain in community practice settings.

Unfortunately, epidemiologic research on morbidity and mortality risks related to opioids has not kept pace with changes in community practice that have occurred over the last 15 to 20 years, so epidemiologists are now playing catch-up in studying health risks related to long-term opioid use. This is important because experience with opioids in the context of acute use -- and there's substantial experience, clinical experience and experimental experience -- that experience with acute use does not adequately inform the effectiveness and safety of long-term opioid use.

Chronic opioid therapy differs from acute opioid use, not only in duration but also dose: concurrent use of other psychoactive drugs and alcohol; onset of physiologic dependence; potential for tolerance; frequency of patient risk factors, including comorbid physical, psychological and

addiction disorders; and the potential for patients to use opioids, to misuse opioids, or to inadvertently use opioids in ways that are not safe. We know little about the implications of these differences for the effectiveness and safety of chronic opioid therapy in community practice settings.

Clinical research and initial epidemiologic studies have identified a spectrum of potential adverse effects of long-term opioid use. Adverse effects of opioid use may affect respiratory, gastrointestinal, musculoskeletal, reproductive, immune, cardiovascular, oral health, neuropsychological, and behavioral systems. Ideally, the safety of chronic opioid therapy would be evaluated by a large, long-term, randomized trial, designed to evaluate the effectiveness and safety of chronic opioid therapy in community practice settings. However, it's unlikely that such a large scale trial will be implemented in the foreseeable future.

So it's informative to compare where we

stand on the extent of clinical trials data for different classes of medications that are commonly used long term in our communities. For example, there are over 750,000 -- three quarters of a million -- person-years of observation in randomized trials, assessing the safety and effectiveness of lipid-lowering agents or statins.

There are over 100,000 person-years of observation in randomized trials assessing the safety and effectiveness of nonsteroidal anti-inflammatory drugs, NSAIDs. In contrast, there are less than 2,000 person-years of observation in randomized trials, assessing the efficacy of opioids for the management of chronic non-cancer pain.

The available randomized trials evaluating use of opioids for chronic non-cancer pain are too small, too brief, and not adequately designed to evaluate the safety of long-term use of opioid medications for chronic non-cancer pain for the less common but still important adverse outcomes.

Gaps in knowledge concerning the

effectiveness and safety of chronic opioid therapy can be addressed now by rigorous comparative effectiveness and safety studies of long-term opioid use by dose, by type of opioid, by duration of opioid use, and by relevant patient characteristics, such as age, gender, and substance abuse history. Epidemiologic methods can also be used to better understand how chronic pain patients are using opioid medications and how these patients are doing in terms of pain and functional status in community practice settings.

Descriptive data on pain and functional status of chronic opioid therapy patients can help us understand variation in how chronic pain patients using this treatment regiment are doing, rather than relying on impressions of clinicians and patients, based on their own personal experience.

In 2009, we completed the largest survey to date of a representative sample of a little over 2100 chronic opioid therapy patients being treated in primary care settings from two large health

plans. We have been using these data to understand how chronic opioid therapy patients in community practice use opioid medications, how they are doing in terms of pain and function, and how patients perceive opioids as a treatment for chronic pain. The large majority of patients in these settings were using average daily doses of less than 50 milligrams morphine equivalents, while a smaller percentage received doses of 120 milligrams or more.

The following slides show how the patients we surveyed were doing in terms of pain and functional status. Now, these are cross-sectional survey data, so they're not intended to evaluate the effectiveness of chronic opioid therapy, but they do shed light on how typical chronic pain patients using opioids long term are doing. These analyses describe pain and functional status of patients receiving low, medium and high opioid doses.

Survey participants were asked to rate their usual or average pain intensity on a zero to 10

scale. As you might expect, we found substantial variation in pain ratings for chronic opioid therapy patients at each dosage level. So this variation of the responses, this is what you were hearing about this morning. This is to be expected. But this also has important clinical relevance when you start thinking about what we should be doing, how we should be managing opioids in the community. Overall, about one-half of the chronic opioid therapy patients rated their pain intensity in the moderate range. About one-third rated their pain the severe range. And about 1 in 10 rated their pain in the mild range.

We also asked survey participants how many days in the past three months they were unable to carry out their usual activities due to pain. Again, there was considerable variation in pain-related activity -- limitation days -- within each dose level. Forty-three percent of patients on low-dose regimens reported frequent activity limitation days due to pain, compared to 58 percent among those using medium dose, and 67 percent on a

higher dose regimen.

This slide shows the current employment status of chronic opioid therapy patients. Among low-dose patients, 18 percent were not working, while among high-dose patients, 46 percent were not working. Persons who were housekeepers were counted as working.

We assessed psychological status using the Patient Health Questionnaire, a well-validated depression scale. A score of 10 or greater on this scale has good sensitivity and specificity for identification of depressive illness. The percent of chronic opioid therapy patients with elevated depressive symptoms was 27 percent among patients using low doses, and among patients on high-dose regiments, it was 61 percent.

So differences in functional status and depression by opioid dose may be due to a variety of factors. For example, patients not doing poorly may be more likely to have their dose escalated. For this reason, these survey data do not evaluate the effectiveness of chronic opioid therapy by

dose.

The take home message is -- the average variation is important, but the central tendency's important, too. So the take home messages are that pain, function and quality of life vary markedly across chronic opioid therapy patients at each dose level. Overall, pain intensity is typically in the moderate to severe range, and pain-related functional disability and depression are common, particularly among patients receiving higher dose.

Within increased opioid prescribing, non-medical use of opioids has increased markedly. The National Survey of Drug Use and Health found that the percentage of persons age 12 or older who had ever used prescription opioids non-medically more than doubled from 1998 to 2008, increasing from 6 percent to about 14 percent. The Monitoring the Future surveys found that the percent of 12th graders reporting non-medical use of prescription opioids in the past year was stable between 2002 and 2011. Around 10 percent of high school seniors reported non-medical use of Vicodin, and about

5 percent reported non-medical use of OxyContin in the prior year.

National survey data indicate that the large majority of persons using prescription opioids non-medically obtain them from a relative or friend for free. It was unusual for opioids to be obtained from a drug dealer or by internet purchase. Survey participants with non-medical opioid use reported that the friends or relatives who provided their drugs usually obtained them from one physician.

These data suggest that opioids available for diversion are often obtained from patients who get them from their usual source of medical care. This raises the question, well, what types of pain patients account for the majority of opioids dispensed in community practice?

We looked at this using our health plan data. We found that 87 percent of the total morphine equivalents were dispensed to chronic opioid therapy patients with chronic non-cancer pain, and that 60 percent were dispensed to chronic

pain patients on higher dose regimens, above 50 milligrams morphine equivalents. Only 13 percent of the total morphine equivalents dispensed in our population in a year were for acute pain or cancer pain management. These results suggest that opioids potentially available for intentional or unintentional diversion in community settings are predominantly prescribed for chronic pain.

So to sum up, long-term use of prescription opioids has increased dramatically in the United States. Fatal drug overdose involving prescription opioids and drug abuse treatment admissions for non-heroin opioid addiction increased concurrently. Pain and function of chronic opioid therapy patients varies. Some chronic pain patients experience low levels of pain and high levels of function in quality of life when using opioids long term, while others have severe pain and low levels of function in quality of life. That said, significant pain-related activity limitations and depression are common among chronic opioid therapy patients, particularly among patients on higher

dose regimens.

Non-medical use of prescription opioids is now common with diverted drugs obtained from friends and relatives who usually get them from one physician. Relative to other widely used medication regimens, data from randomized controlled trials assessing the effectiveness and safety of long-term opioid use for chronic non-cancer pain are sparse.

Given the increases in opioid-related morbidity and mortality, well designed comparative effectiveness and safety studies are needed to better understand the benefits and risks of chronic opioid therapy in the community practice settings where opioids are predominantly prescribed. Prescription opioids are perhaps unique in the extent to which their effects matter to communities, as well as the individual patients and their families.

While the pace of research of chronic opioid therapy has accelerated dramatically in the last five years, research that rigorously assesses the

effectiveness and safety of chronic opioid therapy in community practice settings has been 20 years overdue.

Thank you very much for your attention.

(Applause.)

Questions and Answers

DR. PAULOZZI: Thank you to most of our speakers for some excellent reviews. We have now 10 minutes for questions, and we'll sit up here.

If folks could line up at the micas.

DR. KOLODNY: Hello. This is Andrew Kolodny from Physicians for Responsible Opioid Prescribing. My question relates to whether or not the dramatic increase in opioid prescribing that we've had in the United States over the past 15 years is helping us better address chronic pain?

Do we have epidemiological data from the United States or Denmark, where opioids are also prescribed more liberally, that indicate that there are benefits to the population when opioids are prescribed more freely? We certainly saw the harms associated with the increase in prescribing.

DR. STEWART: That's a hard question to answer because the surveillance systems for chronic pain morbidity just aren't as good as they are for, say, cancer. You don't have a chronic pain surveillance system the way you have for cancer, for instance. Back pain's the area that I know the best. Buzz knows more about headache.

For back pain, the overall cost of back pain care have been accelerating, and there are more procedures being done. And there is some evidence that prevalence of chronic pain is increasing, but it's pretty hard to get a beat on that.

MS. KORNBLAU: My name is Barbara Kornblau, and I'm here representing the Coalition for Disability Health Equity, but my question has nothing to do with that.

As the daughter of a mother who had menstrual migraines and a mother of three adult daughters who have menstrual migraines, when I look at the chart for gender for migraines, I'm wondering if you took into account menstrual migraines, which would start where your slope goes

up and would end where your slope goes down. And then when you look at the SES, more affluent women would be treated for menstrual migraines, whereas people with a lower SES would probably not have access to care.

So I'm wondering if that was a factor in your analysis, if you think that might have a bearing.

DR. STEWART: Are you an epidemiologist?

MS. KORNBLAU: No, but I stayed at a Holiday Inn Express last night.

(Laughter and applause.)

DR. STEWART: So certainly the rise in incidence of migraine begins -- you know, you see a hairy, menarche rise that's fairly dramatic. Menstrual migraine makes up a relatively small share of the overall female prevalent pool. So it comprises probably about 5 percent of all female migraineurs.

MS. KORNBLAU: Could that be diagnostic related? I know that it took my mother years to get diagnosed with menstrual migraines, and I would

assume that it depends. If the average visit is 3.2 minutes to a physician, I don't know that everybody asks those history questions.

DR. STEWART: I don't -- so if your question is menstrual migraine influencing the prevalent picture that we see in the rapid rise, I would say probably not. I would say it's a more -- there's a more general gender-related factor that's probably -- (audio conference interference) -- about which we know very little. There may be a host of other factors that are more strongly associated with female gender that are mediating that, including, obviously, hormonal factors and things of that sort. Because it's obvious, when you look at the rise in incidence, it clearly is post-menarche.

MS. KORNBLAU: Nice little dip where women are having babies and pregnant, not getting the menstrual migraines. Maybe it needs more study.

DR. STEWART: Yes. That dip -- the difference in the prevalence of chronic migraine versus episodic migraine to me is interesting and

suggests that there are perhaps stressors that occur early in life and transition to adulthood that may be I think mediating chronicity. And then there's perhaps a recovery and then an upswing again that more closely parallels the episodic patterns.

DR. DUDA: My name's Lawrence Duda. I'm a general dentist from Albany, New York. I've been in practice for 40 years. I noticed the graph. In 1998, the percentage of opioids take off as far as the prescriptions, the amount of pills out there.

Is there any study in relation -- back in the late '80s, early '90s, I was constantly subjected to marketing from various pharmaceutical companies, particularly in my field of hydrocodone being -- not as addictive, being mildly addictive. And one of the things I did -- and I saw the graph verified that -- is I had stopped writing for Tylenol number 3 and went to the hydrocodone. I was just curious to know if anybody's picked that piece of information up.

DR. PAULOZZI: Yes. I could comment on

that. I think there's some evidence from proprietary data that utilization of opioid analgesics began to increase in the early 1990s. And the emergency department, as it's related to misuse, began to increase around 1995 and 1996. The DEA data only goes back to '97, but the increase really -- and the changes in the attitudes began in the late '80s, I think, and physician practices began. And dental practices began to change in the late '80s and early '90s.

I'm sorry to interrupt. I would also just make an announcement for the people who are attending this conference by conference call, please try to mute your phones or make less noise when you're coming on. I'm not quite sure how one does that, but that's what I was asked to announce to the people on conference.

Go ahead. Next question.

MALE SPEAKER: Thank you. So for the comment and the suggestion I guess for a comparative effectiveness research on the effectiveness and safety of chronic opioid therapy

in the community, some of us who treat patients with chronic musculoskeletal pain follow the WHO step ladder approach. And we only use chronic opioid therapy when patients have had an inadequate response to acetaminophen, non-steroidal anti-inflammatory drugs, and also sometimes let's say the tricyclic and more recent SNRI antidepressants.

So to what should we compare chronic opioid therapy for its effectiveness and safety in these studies, if patients have already -- either not had an adequate response to or have contraindications to those other classes of agents?

DR. VON KORFF: Clearly, a randomized design is always preferable to an observational design. But I think there's some very consequential questions you could answer with observational designs.

You could begin to answer questions about effects of dose. You could develop new information that's needed, comparing effectiveness and harms of short-acting versus long-acting opioids. You might

be able to look at lots of patients quit early on. You may be able to compare patients who discontinue or patients who continue. You probably have to consider reasons for quitting in doing that. There may be some modeling involved in that.

So this is just an area where 5 to 7 million patients at any one time are being exposed to a treatment with an inadequate knowledge base. The importance of getting a much better handle on what the actual benefits are and what the risks are is hard to overstate.

DR. STEWART: Mike, I would also add, in this era of beginning to think about doing trials more efficiently and doing pragmatic trials, where we're trying to integrate the trial -- or I would say focused observation with routine care, I think there are lots of opportunities to gather supplementary data that ordinarily wouldn't find its way to the record, that can help interpret how patients are experiencing these drugs and the side effects.

DR. VON KORFF: In terms of trials, I'd love

to see a tapering trial. I think it's something that may be possible to pull off, or dose-reduction trial. It would be easier to do on a large-scale basis than a trial where you're initiating patients and following them over time.

DR. PAULOZZI: I'm sorry. I was asked to limit the questions to 10 minutes, so this will have to be the last question. I believe you were next.

DR. CHAUMONT: Good afternoon. My name is Jorge Chaumont. I am a pain medicine specialist in Florida. My question is a two-prong question.

What is your opinion, particularly in view of the data that you present with a risk of the opioids -- with the --

DR. PAULOZZI: Could you get up to the microphone?

DR. CHAUMONT: -- with recommendations such as these. For instance, this is a family practice. This news journal I received a couple of weeks ago with an OxyContin advertisement with recommendations for the family physician to those

patients, up to 160 milligrams of oxycodone per day. You were alluding to the primary care setting, where opioids are most likely prescribed.

I wonder if your opinion has in any way changed from the time of this implementation back in the '90s, and if there is going to be any change in view of the new data that is resurfacing or that has surfaced in the last few years, showing the perils and the risk of this.

DR. VON KORFF: You now, I'm not -- could you restate the question?

DR. CHAUMONT: Okay. And I'm sorry, because it's a complex issue. And I am --

DR. VON KORFF: Well, I caught most of it. Just give me the question.

DR. CHAUMONT: The question is, should we be inducing family practitioners to prescribe 160 milligram dosing of OxyContin in a primary care setting, having pictures of patients, photographs of patients -- they're smiling. This one is for 5 milligram, and this is for 80 milligram twice-a-day dosing. Should those recommendations

be liberally made in view of the present recommendations?

DR. VON KORFF: First of all, I'm not a physician, but I'll just tell you as a researcher what my attitude -- I've got a couple thoughts on this. One is, primary care physicians tend to prefer conservative therapies, so they tend to prefer low-dose regimens. That's reflected in our data.

The second observation is I think that primary care, much more than specialties, has embraced evidence-based medicine. They've embraced it, really, at our place for the last 20 years, but nationally for the last 10 years at least.

So if you're going to be recommending a treatment regimen or a protocol, there really should be some evidence for it. And dose escalation recommendations I would say, there's not really good evidence for that. With the growing evidence of dose-related risks, my tendency would be to recommend caution as a researcher.

DR. PAULOZZI: Okay. Thank you very much.

This concludes the session. Thanks again to our speakers.

(Applause.)

Open Public Hearing

DR. THROCKMORTON: Thanks, Len, very much.

While they're sitting down, we're going to do a little bit of transitioning here. We'll be moving now from discussions about what we know about the mechanisms of pain, what we know about the epidemiology of pain and its treatments in America today, to treatment of chronic pain.

As Dr. Rappaport and I talked about how to structure this meeting, we thought it was very important to begin that discussion by listening to the people, the advocacy, the advocate groups that had a stake in the use of these medicines for the treatment of chronic pain. And so for the next session, the session remaining today, we wanted to hear from those groups.

What I wanted to do, and what I see we've done, is we've turned the microphone around. I'd really like to ask the people that are going to be

making their statements to make their statements to the audience because I think it's more important that you make that to them.

I'm going to be sitting up here mostly in a refereeing role, something like that, and I'm going to have somebody sitting down with you as you make your remarks. You have the two minutes that each of you have been given. I'd ask you to please stay within those two minutes, if at all possible, so that we can stay -- well, as off time as we are at present, and get the session done today.

I think we started a very good conversation already about people's views about the treatment of chronic pain. We'll have an opportunity for people that didn't get a chance to ask their questions today to raise those questions tomorrow.

I don't know. Mary, how would you like to structure it?

(Pause.)

DR. THROCKMORTON: So I will read the names, and I guess I'd ask you to come to the microphone there by the front and speak to the audience,

please, and look forward to hearing the things that you all have to say.

I think you all have the list, so you can see, roughly speaking, where your names come in that order. The first person is Cindy Steinberg from Massachusetts Pain Initiative.

MS. STEINBERG: My name is Cindy Steinberg. As he said, I am the policy chair with Massachusetts Pain Initiative.

I want to share a story about a young man named Scott. He's outgoing, loves cars, playing drums, and his job is a mechanic. Scott now endures daily pain in his mid-back that feels like someone is repeatedly stabbing him with a knife and twisting it.

Three vertebrae in Scott's thoracic back were fractured in a crush injury while working under a vehicle. After the accident, his wife moved out, and he lost his job. Drumming sessions and driving his Corvette were no longer possible. Doctors said the bone fractures had healed, yet Scott's pain continued unabated. He felt hopeless

and isolated.

Having the kind of disabling pain Scott lives with is not uncommon. I know because my accident from a crush injury led to similar, debilitating pain. Through this support group I founded 12 years ago, I met Scott and more than 200 chronic pain sufferers.

Having chronic pain is like being sentenced to a life in prison. You are a prisoner in your own body, but it's worse than that. You are a prisoner who is subjected to torture 24/7. Our country frequently debates the morality of torture for prisoners who have killed thousands. But I ask, what kind of moral society do we live in when we are talking about removing or severely restricting a treatment option that we know lessens this tortuous existence for hundreds, thousands, and perhaps millions of Americans?

Opioid analgesics do not help everyone with chronic pain. And when they do, they don't completely relieve the pain. Scott has been on a long-acting opioid for 10 years. Other than

limiting time spent upright, it is the only treatment that has helped him. While he's unable to work or play his drums, the medication has allowed him to regain pursuits that once again gives him enjoyment, like playing the guitar and caring for his young niece and nephew. The majority of people who use opioid medications use them safely and appropriately. These medicines offer relief from the horrific torture that comes to plunder their whole existence.

You will hear many impassioned pleas today in opposition to the use of opioids for chronic non-cancer pain. I ask that you please remember Scott as you listen and do not further restrict or renew this important treatment option. For millions of Americans who live with pain, this means the difference between a life worth living or not.

(Applause.)

DR. THROCKMORTON: Andrew Kolodny, Physicians for Responsible Opioid Prescribing.

DR. KOLODNY: My name is Andrew Kolodny.

I'm president for Physicians for Responsible Opioid Prescribing and chair of psychiatry at Maimonides Medical Center in New York City.

Opioid overprescribing is fueling an epidemic of addiction and death. This began 15 years ago in response to a campaign that misinformed doctors and patients. Many now believe that long-term use for chronic pain was proven safe and effective, but for most patients, evidence suggests that it's not safe or effective.

Some say carefully selecting patients without risk factors makes it safe. This is not true. Opioids are inherently addictive. Patients without a substance abuse history can become addicted. Close monitoring can lead to early identification of addiction, but it doesn't prevent it. The point at which a prescriber recognizes addiction, the damage has been done. The patient has developed a devastating illness that may kill them.

There is something you, FDA, can do about this public health crisis. You can close a

loophole on opioid labels that leads to overprescribing. An indication that reads moderate to severe pain is inappropriate. It implies a determination by FDA that long-term use is safe and effective for fibromyalgia, for chronic headache, for other conditions where experts advise against use of opioids.

The label is a billion dollar give-away to drug companies at the expense of the public's health. FDA must fix the label and must let our medical community know what every expert in this room knows, which is that opioids have not been proven safe and effective for long-term use in chronic pain.

DR. THROCKMORTON: Thank you.

(Applause.)

DR. THROCKMORTON: Pete Jackson, also from PROP.

MR. JACKSON: I'm actually Pete Jackson with Advocates for the Reform of Prescription Opioids or ARPO. I'm also the parent of a wonderful girl named Emily (ph), who in 2006, at the age of 18,

lost her life to a single OxyContin pill swallowed whole. Out of my daughter's tragedy and those of many other people across the U.S. and Canada, ARPO was formed. We represent bereaved families and families struggling with addiction across two countries. Our outreach is now in the thousands and is growing.

ARPO's mission is to end the opioid epidemic of death and addiction by ensuring that opioids are regulated, marketed, prescribed and used in an evidence-based manner. The majority of the lost loved ones, with for whom we grieve, were once pain patients. ARPO believes the following concerns should exert a strong influence on prescription opioid use.

First, the tragic consequences of heavy opioid marketing and prescribing are well documented.

Second, opioids have not been proven safe or effective for treating chronic non-cancer pain.

Third, adverse outcomes affect all categories of users, including patients.

Fourth, not all non-medical users are recreational. Many self-medicate for physical pain. For instance, many non-medical users are former pain patients. There is no bright line between pain patients and non-medical users.

Fifth, ARPO has strong concerns with the lavish manner in which opioids are being prescribed. Opioid prescribing is increasing for young people who are particularly vulnerable; is most common in people with mental health and substance use disorders; is increasingly following minor surgery; is heavily used to treat fibromyalgia patients; and is associated with higher mortality rates and more falls and fractures in seniors than are NSAIDs.

I could go on, but all of these trends have had serious adverse consequences. ARPO believes that the best solution to the problem is to make the label and changes Dr. Kolodny just alluded to. Thank you.

(Applause.)

DR. THROCKMORTON: Thank you, Pete.

Daniel Carr, from the American Society of Anesthesiologists.

DR. CARR: Good afternoon. My name is Daniel Carr. I'm a professor of anesthesiology medicine and public health at Tufts University School of Medicine, and a member of the American Society of Anesthesiologists Committee on Pain Medicine. ASA is delighted to participate in the agency's discussion on the use of opioids in chronic painful conditions.

The insight that chronic pain is a distinct clinical entity whose diagnosis and treatment require specialized expertise originated with the anesthesiologist John Bonica in the 1940s. Our fundamental methods for assessing patient reported outcomes in analgesic trials, including the assessment of pain intensity and placebo controls, follow directly from the work of the anesthesiologist Henry Beecher in the 1950s.

Remarkable advances in understanding preclinical and clinical chronic pain states and their treatments reflect the ongoing labors of

generations of preclinical and clinical investigators in departments of anesthesiology on pain mechanisms from the synapse through the living human brain. Detailed mechanism-based descriptions of chronic pain as a disease state per se have been prepared by world leaders in anesthesiology, particularly Michael Cousins, the past president of the International Association for the Study of Pain that Bonica founded in 1973.

ASA's updated 2010 practice guidelines for chronic pain management synthesized available evidence from controlled clinical trials of opioid and other drug and non-drug therapies, supplemented by input from pain committee members and other clinicians in surveys and open forums. I shall briefly summarize the principle conclusions, and I'll submit the guidelines with ASA's written comments.

The guidelines recommend that individual multimodal interventions be used to care for patients with chronic pain, and pharmacologic management may be used as part of the multimodal

treatment strategy. Specifically, the guidelines state that anticonvulsants should be used for patients with neuropathic pain.

Tricyclic antidepressant and serotonin norepinephrine reuptake inhibitors may be used for a variety of patients with chronic pain. Selective serotonin reuptake inhibitors might be considered for patients with diabetic neuropathy. For selected patients, NMDA receptor antagonist, NSAIDs and topical agents may be used, and --

DR. THROCKMORTON: Dr. Carr, are you almost done?

DR. CARR: I will conclude in the next 45 seconds.

DR. THROCKMORTON: Okay. Your time is up, so please hurry.

DR. CARR: For selected patients, NMDA receptor antagonists, NSAIDs and topical agents may be used. In regard to opioids, the guidelines state that extended-release oral opioids are efficacious for patients with neuropathic pain, or back pain, and are available in various

formulations. A meta-analysis indicates controlled or extended-release opioid therapy provides effective pain relief for patients with low back or neuropathic pain for varying assessment treatments.

We agree with many in the pain treatment community that additional research should be conducted on the long-term efficacy of opioids for chronic pain. Further, access to opioids must be balanced with efforts to reduce the misuse of use and diversion of these medications, particularly those obtained through medical prescriptions.

Fundamental questions bearing upon the benefit-to-risk ratio of opioids and other treatments for chronic non-cancer pain must be resolved, such as the percentages of patients of various ages and genders will become tolerant, dependent upon, or addicted to opioids during long-term therapy. This effort must be accomplished in a comprehensive fashion, accommodating individual variability, the diversity of our nation's population, and supplementing results from randomized control trials with

outcomes data on treatment effectiveness in everyday settings of care.

Thank you.

DR. THROCKMORTON: Bob Twillman, American Academy of Pain Management.

DR. TWILLMAN: My name is Bob Twillman. I'm the director of policy and advocacy for the American Academy of Pain Management, a professional organization that promotes an integrative model of pain care, one that is person-centered, individualized, and brings together all appropriate therapies to reduce pain and achieve optimal health and healing.

For some, opioid analgesics, when prescribed as part of a comprehensive treatment plan, can significantly reduce pain and restore function. Of course, we understand that these medications carry serious risks, and we must ask questions such as, for whom do they provide this benefit and to what extent? What are the risks associated with this treatment? And what measures need to be taken to ensure that these medications do not get into hands

of those who would abuse and divert them?

Unfortunately, we're seeing that too often the answer to the last question is to substantially reduce the supply of these medications. These measures have resulted in a tyranny of the minority in which the improper and often illegal behavior of a small minority of people who misuse prescription pain relievers deprives people with pain of a treatment that many find life-enhancing and even life-saving.

We've seen this happen in states such as Florida, where a resident recently asked for my help in getting his prescriptions filled after he tried and failed at 35 pharmacies. And he was not alone. In an online survey of 130 Floridians who had prescriptions for opioids refused by pharmacists, 57 percent of respondents said that they had to visit 10 or more pharmacies to get their prescriptions filled. Eighty-five percent of these people completely ran out of medications, and two-thirds of them went without for at least three days, suffering increased pain and opioid

withdrawal.

We've been prescribing policy treatments before conducting a thorough diagnostic workup of this complex, multidimensional problem, one that surely will not be remedied by quick-fix solutions. Dramatically cutting the supply of opioids, hoping to stop illegal use, harms legitimate patients who take them responsibly and legally, and is not the answer. We all need to find the sensible middle ground and should not allow the misuse of prescription drugs to undermine the use of these vital medications by people with pain.

DR. THROCKMORTON: Thank you.

(Applause.)

DR. THROCKMORTON: Betts Tully.

MS. TULLY: Good afternoon. My name is Betts Tully. I am medically considered a chronic pain patient, etiology involving the lower back. I became medically addicted to OxyContin in 2001, after which my life became a nightmare, taking me eight years to get myself off of all prescribed analgesics and two more years to recover from the

effects.

I have confidence that I am representing the thousands of patients who have been harmed by an inadequate and unsafe delivery system of providing pain relief to chronic pain patients. Most of these people -- these people that I'm talking about -- have no longer a voice to address you due to the brain damage and an unwanted death.

The two notions that pain is undermedicated in this nation and less than 2 percent of pain patients become addicted, are false, and have always been false. These two notions have driven the crisis that has brought us all here today.

Nora Volkow, director of NIDA, said either we are a nation in severe pain or we are overprescribing. She also said, being honest, many physicians have not been properly trained on how to prescribe opiate medications.

I am hoping that all of you will be as forthright and honest as Ms. Volkow was and address that fact, that misinformation. An untrained physician has led to a disaster. The FDA needs to

take action now, not later, not another 10 years. That's a horrible idea that we would take 10 more years to continue the research that should have been done in 1995, before this started.

Please, this should no longer be a debate. As a pain patient, whether in acute or chronic condition, I have a right to expect my physician has the training and education that is required to make the serious and possibly life-altering decision to introduce narcotics to my system long term. I want him to know what he's doing. I should have expected that. And there are too many people who are not here today who also expected that, believed in it, and trusted in it.

Please implement the immediate label changes that will ensure that only trained and properly educated physicians are allowed to use these class of drugs. Chronic pain patients who fear being untreated cannot be the foundation for your recommendations. Science, safety and best practices must be. We are all in this together.

I am a chronic pain patient. I understand

the chronic pain, but I don't want to be brain damaged. I don't want to be dead. I want a trained physician to know what he's doing, and it needs to be based on science. Please address this in a way that we can all live with the results.

DR. THROCKMORTON: Thank you.

(Applause.)

DR. THROCKMORTON: Kathleen Zinno.

(No response.)

DR. THROCKMORTON: Lawrence Duda, D-U-D-A, Physicians for Responsible Opioid Prescribing.

DR. DUDA: I was up for a question before. My name is Lawrence Duda. I'm a general dentist practicing in Albany, New York. I currently teach clinical dentistry at St. Peters dental residency program. And I'm also affiliated with Baldwin Research Institute. It's a small upstate New York private alcohol and drug addiction research and treatment center.

In the mid '80s, I broke my forearm and wrist. My physician prescribed Tylox for one week for pain. Early in the year of 1996, more than 10

years later, the State of New York, utilizing their professional assistance program, asked me to stop using drugs and enter into recovery, and I did. After a few months of treatment and a life-threatening seizure, one week in the hospital, the PAP, the Professional Assistance Program, said I could restart my dental practice, and I did. I have never been addicted since. Sixteen years of my life has been restored and never better.

Some of my concerns with the current opioid prescribing relaxation. Addiction can be acquired in as little as five to seven days of continual use. These are all cited by the way. The use of opiates for treatment of chronic pain is not definitive. I personally have observed that an increase in dosage is needed after five days.

Long-term use of opiates is operative in increased dental root decay, periodontal disease, candidiasis, thrush. And a real problem for me, I cannot get patients numb anymore. I've been at this for 40 years. We now have new novocaines called articaine or septocaine. Any dentists in

here might know that. And it's a pain, because their systems are just terrible. I personally prescribe minimal dosage because of hoarding and consequent theft. And I try everything possible not to introduce my patients to opiates and to trigger a genetic predisposed chemical dependency issue.

I remember my very first opiate experience to this day. Thank you.

(Applause.)

DR. THROCKMORTON: Thank you. Jorge Chaumont.

DR. CHAUMONT: Good afternoon again. The last 20 years should be considered a failed trial of opioids in the treatment of chronic pain non-malignant pain. We do not have evidence that benefits outweigh risks. The FDA must create a precise on-label indications to communicate this fact.

I earlier stated my name, Jorge Chaumont. I'm a board certified anesthesiologist and pain

medicine specialist. I practice solely the treatment of chronic pain, and I have for many years. Early on, we were heavily promoted through advertising, marketing campaigns, experts in the field, and much lobbying to persuade us from the widely-held caution that treating chronic pain with opioids was a myth. Physicians were persuaded to treat pain with as much opioids as was needed to meet patients' complaints.

The resistance to this change in using opioids was mitigated by the premise that they were safe for long-term use, and the risks of addiction, misuse and diversion were low. Given the very quality of life and improvement in function promised, we became advocates despite that there were no robust scientific data to support these claims.

Twenty years have passed, and I now rarely offer opioids to my patients, given the mortality, paradoxical increase in pain, cognitive impairment, endocrine, sleep and GI disorders, addiction, tolerance, misuse, and diversion. Risks rarely are

convincing to warrant their use.

Pain is endemic and multifactorial, indistinguishable from suffering. It is futile and dangerous to treat suffering with narcotics. I empower my patients with the knowledge that modulation of pain is controlled by the brain. Cognitive -- we have other therapy and other safer medications, exercise, and intervention of pain management, which is my specialty; rarely use as the last resort. Although far from perfect, this approach has been a safer alternative to opioids in improving my patients' quality of life and function.

Lastly, I'd like to tell you that being from Florida, my largest problem is from referrals from primary care, where patients already have addiction problems and are highly dependent on opioids, and it makes my work far more difficult because as the patients become detoxified from these drugs, they mistake their withdrawal signs and symptoms of withdrawal with more pain, making it all the more difficult.

Thank you for your time.

(Applause.)

DR. THROCKMORTON: Thank you.. Rene Cabral-Daniels.

MS. CABRAL-DANIELS: Good afternoon. Thank you for the opportunity to present comments on behalf of the National Patient Advocate Foundation. NPAF is a nonprofit organization dedicated to improving patient access to care services through both federal and state policy reform. Its mission is to be the voice of patients who have sought care after a diagnosis of chronic debilitating or life-threatening illnesses. The advocacy activities of NPAF are informed and influenced by the collective experiences of patients who receive direct sustained case management services from our companion organization, Patient Advocate Foundation.

In 2011, PAF resolved over 110,000 patients cases and has received more than 5 million additional inquiries from patients nationwide. And PAF encourages FDA to consider the efficacy of

analgesics in the treatment of chronic non-cancer pain by adopting a number of strategies.

One such strategy might be partnering with the patient advocate community and public/private partnerships to educate and thereby elevate the ability of patients to provide meaningful input throughout each stage of FDA's deliberations on this important issue.

A number of important points have been raised today that highlight the importance of patient involvement. Please follow earlier representers' recommendations that this issue consider the heterogeneity of the patient experience. Thank you.

(Applause.)

DR. THROCKMORTON: Thank you. Lynn Webster.

DR. WEBSTER: Hello, everyone. I'm Lynn Webster, president-elect of the American Academy of Pain Medicine. I reaffirm the academy's commitment, first and foremost, to patient safety. We define patient safety to include educating patients and physicians about the appropriate use

and potential risk of pain medications. But to us, patient safety also includes protecting patients from the harm that can come from untreated chronic pain, such as disability, compromised quality of life, and increased risk of suicide.

Opioids are not the solution for every patient or every problem, but they are an important element in the comprehensive treatment of a subset of patients with chronic pain. To date, short-term clinical trials of opioids do show pain relief for some patients who otherwise would go without such relief. The real question we must address is long-term efficacy and effectiveness of opioids for chronic non-malignant pain along with their potential risks.

This question has not bee satisfactorily answered. We need to find these answers. But this will take a commitment from groups such as NIH, to study the long-term effectiveness of opioids for pain and support the development of new, safer medications.

Pain is multidimensional, and people respond

to medications in different ways. Individual response to medication differs just as widely as the physical appearance from one person to the next. According to the recent report from the Institute of Medicine, 100 million Americans suffer from chronic pain. Their suffering and focus on safety should drive everything we do. By studying how to safely treat their pain better, we can improve their lives in countless ways.

Thank you very much.

(Applause.)

DR. THROCKMORTON: Thank you. Colonel Walter Craig.

COL. CRAIG: Good afternoon, ladies and gentlemen. I'm quite sobered by the discussion today. I've been using opioids for 14 years now. As he said, I'm Colonel Walt Craig. I'm a volunteer for the Center for Practical Bioethics in Kansas City, Missouri. I speak for the chief executive, Mr. John Carney, who must remain home due to family health issues. He sends his regrets. He'll submit formal testimony by writing. As a

matter of full disclosure, the center is reimbursing me only for my expenses, with no others.

The center's mission is to raise and respond to ethical issues in health and health care. It's founded in 1984. The center has advocated for the seriously ill and dying, consistent with the patient's goals and values. Programs have focused on advance care planning, end-of-life decision making, and improved care for those suffering chronic pain at all stages of life. The center is known for work in patients' rights, institutional ethics, the protection of human research subjects, and an expanding palliative care for those living with chronic disease.

Mr. Carney asked me to share with you the center's core belief that effective pain management is a moral imperative, and furthermore, it is a professional and clinical responsibility and a duty of personnel and the healing professions. The center has shared its work in this area with devoted healthcare providers, professional

societies, law enforcement agencies, and other entities to include people living with pain and their families.

As one of over 100 million Americans -- that figure keeps coming up -- who live with chronic pain everyday, I'm grateful for the work the center does.

Now, I'd like to transition to my presentation.

DR. THROCKMORTON: Thank you.

COL. CRAIG: I've been a below-knee amputee for the past 14 years. I have constant stump pain that can adversely affect my quality of life if not properly managed by the judicious use of opioids. This experience addresses the agenda topic of efficacy of analgesics in treating CNCP. I'm fortunate to be under the consistent care of a pain management physician.

More to the point, the prudent use of Kadian and oxycodone opioids have been a lifesaver to me, 100 milligrams of Kadian a day, 20 to 40 milligrams of oxycodone a day. Now, however, the use of

oxycodone is a particular concern to me in that I have a fear of addiction, a fear based on seeing, firsthand, soldiers addicted to heroin in Vietnam. The battalion to which I was assigned experienced fraggings, assault upon officers and NCOs, as well as the murder of a young Army captain in my battalion. Given this experience, my personal pain management goal is to use only just enough to maintain a good quality of life. I seek titration downward wherever possible.

In my own opinion, I think some of the challenges wounded warriors are seeing is a lack of provider consistency. And that population provides a good example of one that might merit further study because their providers are constantly moving and the soldiers are constantly moving. I believe the doctor/patient relationship must never be held captive to the whims of politics of the season or to non-professionals attempting to mandate treatments. I believe that tampering with a properly managed medical service delivery system could set the conditions for increased drug abuse

as an unintended consequence of ill-founded actions.

I believe a patient must recognize the dangers as well as the benefits of any drug use. They should educate themselves about the drugs they are taking and take personal responsibility for their own well-being, and above all, to be honest with their pain management provider as well as themselves. Thank you.

(Applause.)

DR. THROCKMORTON: Thank you. Harris Silver.

DR. SILVER: Good afternoon. I'm a retired head and neck surgeon, and I've dealt with chronic pain for 22 years now. I was in a car accident, and as a result, I've had four ruptured discs in my neck, requiring five surgeries that began in 1990. My third disc ruptured in 2007. I had a cervical fusion surgery, which failed and left me with chronic burning pain and taking increasing doses of Percocet.

A year later, I had a revision surgery on my

neck, which required two rods. And I ended up eventually on OxyContin, 120 milligrams a day, and I was still on some Percocet. After five brutal months of getting off the OxyContin, my pain was still bad, so I was unable to get off the Percocet.

Three months more then passed with me no better, so my pain specialist offered me a nerve stimulator and recommended that I return to OxyContin. My pain specialist also reassured me I was not addicted to the pain meds, yet I obsessed about my next dose. I was very anxious and depressed. I functioned poorly, and I struggled to maintain my Percocet dose.

Then I consulted with two addiction and pain specialists, who explained to me, first, that I was addicted, and that the drugs' effect on my brain was distorting my ability to judge my pain level as well as my response to the medicine. They also said that I likely had a hyper perception of pain called hyperalgesia and that the pain medicine may be making my anxiety worse.

Despite being terrified of tapering off the

Percocet, I took both doctors' advice to get extra help to do so, and engaged intensively in multiple non-medication treatments for pain. Two months later, I was off the Percocet, and my physical pain was about the same, but my emotional state and activity level were much better. Another month later, my pain was much improved, and I gradually went back to work as an epidemiologist.

I continue to have significant neck pain at times, but I can live with it, without opioids. And I have a good quality of life thanks to the pain-coping skills that I've learned and the anti-inflammatory medicine I take.

I'd just like to say one more thing. I'm an advocate now for people with substance use disorders and for the reform of appropriate choice in prescribing opioids, especially long term, to patients, and the FDA labeling reforms described by Dr. Kolodny. Thank you.

(Applause.)

DR. THROCKMORTON: Thank you. Mark Odden.

MR. ODDEN: Good afternoon. My name is Mark

Odden. I'm a certified registered nurse anesthetist, who's rural Iowa anesthesia practice includes pain management services. I am pleased to represent and speak on behalf of the American Association of Nurse Anesthetists, which represents 44,000 CRNAs and student nurse anesthetists who deliver more than 32 million anesthetics in the United States each year. Pain management is a critical aspect of the anesthesia care continuum providing acute and chronic pain management services, and this is within the CRNA's professional scope of practice.

Today, we briefly touched on known sources of chronic pain, the populations affected by this, and the trends of current pharmacologic use. Chronic pain develops from a variety of sources we heard today. Additional sources, which we did not explore in any extent, were the contributing factors of the chronic conditions: injuries, obesity, smoking, and societal factors which plague us all. Lack of access to pain care for treatment during the acute phase may also lead to chronic

pain states.

In Iowa, over 12 percent of Iowa residents live below the poverty level. Almost 15 percent are 65 and older, and 17 percent are Medicare beneficiaries. Sixteen percent of our Medicare beneficiaries are also Medicaid recipients. Our pain practice cares for many people who fall into many of these categories. Without pain care services, the patients that we have suffer from many things. They have multiple things that can occur to them in addition to their pain, such as traveling long distance, having to seek care in a major medical facility, costly surgery, institutionalization, or a combination of all of those.

Current trends and pharmaceutical use, we rely upon on this body of research and evidence-based guidelines to inform our clinical practice. We assess our patients and their unique situations and explore and develop a multimodal treatment plan, which involves education, physical therapy, adjuvant medications, and interventional

pain management techniques. While we do not prescribe opioids frequently, we do use them with other active therapies. And, yes, they do have a place in our pain management care.

Ensuring access to pain care involves hearing from a wide spectrum of patients, healthcare professionals, industry representatives, and those individuals whose work depends on these services. The American Association of Nurse Anesthetists applauds the FDA for holding this workshop, and we appreciate hearing perspectives of patients who are in pain, those that treat pain, and the researchers involved in this. The AANE looks forward to working with you in the future as we examine ways of handling chronic pain. Thank you for the opportunity to speak today.

(Applause.)

DR. THROCKMORTON: Thank you. Bernard Mullen. Mr. Mullen?

(No response.)

DR. THROCKMORTON: Larry Golbom.

MR. GOLBOM: I am Larry Golbom, and I do the

prescription addiction radio show, "Breaking the Silence." I'm also responsible for the petition called banoxyContin.com. I'm here to make a public disclosure. Neither the radio show or banoxycontin.com is under any Senate finance committee investigation.

To the pain patients in attendance, we all wish you the finest medical care possible. And I hope all the speakers are here to help us find a solution to the addiction and deaths the legal narcotics are creating.

Folks, we've got some elephants in this room. For the pain patients, I'm concerned about drug addiction. Drug addiction. Drug addiction. Statistically speaking, many pain patients become drug addicts. One of the elephants is the FDA's refusal to separate proper medical care and addiction. The other elephant, the Senate Finance Committee investigation.

How can the FDA allow people in this room to publicly present themselves and not disclose they were either mentioned in the Senate investigation

or they have been affiliated in some way with groups being investigated? I hope, if we have media in this room, you cover the issue of the Senate investigation as it relates to this meeting.

Addiction, deaths, lives destroyed, people being investigated over marketing and over distribution, and the FDA expects the American people to take this meeting seriously? In due respect to the hardworking FDA employees, dedicated FDA employees in this room, the workshop structure, in sincerity, makes the entire FDA look extremely incompetent. Until the elephants are discussed by the FDA, I don't belong at this meeting.

DR. THROCKMORTON: Thank you. Shani Weber.

MS. WEBER: Hello. I'm Shani Weber. No worries, it's a hard name.

DR. THROCKMORTON: Apologies.

MS. WEBER: I have Ehlers-Danlos syndrome or EDS, which is a genetic connective tissue disorder. What it means is that my body produces defective collagen. If you're not familiar with collagen, it is in all body systems in the body. There are more

than six types of EDS. And the type that I have is hypermobility type. What that also means is that I have frequent subluxation and dislocation of the joints in my body. I subluxate and dislocate my shoulders, my scapulas, my ribs, and my knees. Yes, ribs can dislocate, and it is not comfortable.

If any of you have ever had a dislocation, it's very painful. And when this happens on a daily, weekly, forever way, it takes a lot of pain management resources.

EDS is rather unique in the medical world in that it's both chronic and acute pain that the patients feel. And of course as a genetic condition, there is no cure for EDS.

For three years, I have carefully taken low-dose opiates as part of my pain management arsenal. I do take a daily extended-release opiate, as well as a short-acting opiate for breakthrough pain. Those are usually called dislocations for me. My dosage in those three years has not become higher. My usage is fairly stable, depending upon how many dislocations I've

had.

I also use my tinge unit, heating pads, ice, massages, physical therapy exercises, biofeedback, meditation, good sleep practices, good diet, distraction, Epsom salt warm soaks. I have a full arsenal of pain management strategies, and the non-medicinal options are very valuable to me. But without the opiate medication as my foundation, I cannot be productive or even functional.

With opiates I can be productive. I have two fantastic children, and they deserve a mother who can be their biggest cheerleader and can be their most invested teacher. I can co-lead a support group for others with EDS and moderate a support forum.

Thanks to the careful use of opiates to manage my EDS symptoms, I can be a mother, a wife, and an active community member. The facts are, my EDS causes high pain levels, and opiates allow me to both figuratively and literally have hope of having a life. I appreciate you listening to this person with Ehlers-Danlos syndrome. Thank you.

(Applause.)

DR. THROCKMORTON: Thank you. Heather Pierce. Got that one right.

MS. PIERCE: Hi. My name is Heather, and I am here to put a face on chronic non-cancerous pain. I'm a mom of two beautiful children, an educator, a volunteer, a support group organizer. I have Ehlers-Danlos syndrome, with almost daily injuries and have responsibly taken opioid medication at the same dose for five years, thanks to great doctors and a determination for me to support my body in every way possible.

My medicine is part of a toolbox that gives me control over my daily function and needs. My faulty connective tissue makes this merely impossible. My toolbox includes other vital techniques, such as meditation, constant physical therapy, supplements, aqua therapy, healthy habits, diet, and more. Removing even one of those things, including the opioid medication, from this carefully constructed toolbox subjects me to a life of dysfunction, unrelenting acute and chronic pain.

I am frustrated by prescription medication misuse. I see the need for education, supervision, and best practices. But now, some of these regulations and the lack of literature on people like me have great doctors and pharmacists nervous to treat us or even unwilling to help. This is blocking pain medication access for those who legitimately and responsibly use it.

These stories are equally devastating. People are being robbed of their functional lives, desperate for help, as help is just beyond their grasp. I myself was there. I was misdiagnosed with fibromyalgia for 14 years. I was told my pain from acute injuries were because I was over reactive. No one claims that now. I lived and irrevocably deteriorated with this untreated pain and ignored injuries until it became evident that there was more to the story, leading me to a geneticist. I should note also my grandmother was diagnosed at 82, after being told she had fibromyalgia.

Like others, I am determined to keep my life

valid and meaningful. Ehlers-Danlos is genetic, making me a role model for my children who are on their own journeys. To do this, I need access to appropriate care, including pain medication. It gives me a chance to be the mom and person I know I am, regardless of the obstacles my body is continually presenting me with.

During this workshop, as you review data and new discoveries, please remember, chronic non-cancerous pain consists of people like me, including those with Ehlers-Danlos syndrome. I carry with me the stories of my friends who also have pain medication in their toolboxes. They wish they could be here, too. They want you to know we are concerned that our stories are being lost in the clatter. We want you to know we are out here. We're leading more functional lives with treatment, and we hope researchers catch up with our part of the story soon.

Thank you for this opportunity.

(Applause.)

DR. THROCKMORTON: Thank you. Melody

Meginity. I may have that wrong, too.

MS. MEGINITY: Hi. My name is Melody, and I have Ehlers-Danlos syndrome. Also known as EDS, Ehlers-Danlos syndrome is a genetic connective tissue disorder, which you've already heard. And I'm here today to discuss the importance of adequate pain management for those like myself who suffer from chronic pain.

A typical EDS'r learns to self-manage their pain at an early age, avoiding activities which exacerbate symptoms, distraction from pain. Meditation and other over-the-counter medications are some initial tools used by EDS'rs. As pain progresses, additional tools, such as biofeedback, physical therapy, tinge units, and prescription medications are needed.

As we have heard today, it is rare, if not impossible, for a single approach to adequately alleve pain. It is imperative that all tools are available for the treatment of pain in patients, improving their ability to function as mothers, fathers, students, employees, and members of our

society.

When I'm in pain, I dream of pain. I hope to make it through the day. I make no plans. When my pain is managed, I dream of my future for new experiences, I hope, and plan time with my loved ones. My main concern here is that the quality of life and quality of care remain the center of these discussions to educate, rather than intimidate, both doctors and patients, and for patients to take ownership of their care. I ask this for myself and for my children who face similar difficulties in the future. Thank you.

(Applause.)

DR. THROCKMORTON: Thank you.

MS. PEOKOWITZ: Good afternoon. I'm Rebecca Peokowitz. I'm 60 years old. For the first 55 years of my life, I didn't have chronic pain because the doctors, my parents, all the adults in my life told me I was a drama queen, an over-reacter, a malingerer, a drug seeker.

How many people in this room are primary care physicians? Please put your hands up.

(No response.)

MS. PEOKOWITZ: Not one primary care physician in this room. The primary care physicians hold my life in their hands. I also have Ehlers-Danlos.

On April 2nd, I had spinal surgery. That was my 26th surgical procedure in my life. But until five years ago, when I was diagnosed with Ehlers-Danlos, what I was told was that I was a non-compliant patient, that I didn't follow doctors' orders, that I got up and moved when I should have laid still, that I laid still when I should have gotten up and moved. It was always my fault.

How many specialists are there here who actually see patients and prescribe medications? Please put your hands up.

(Hands raised.)

MS. PEOKOWITZ: Seven. Anybody else? Seven people who are actually prescribing medications. I have some answers for you. If you're a specialist and you supervise primary care physicians, they

need to be taught how to prescribe medications. They need to be taught that there is such a thing as a clinical pharmacologist who can help me manage my medications. I don't want to be told again by a primary care physician, who prescribed and prescribed and prescribed for my volatile blood pressure, which is another side effect of EDS for some people -- who prescribed so many medications that I was literally following asleep at red lights. And my mouth was so dry that I couldn't speak to my students. And when I went back to that primary care physician, the primary care physician said, "Suck on lemon drops."

Please, researchers, media, get the word out. It's got to be collaborative. We've got to use the tools, and you have to stop being the tools of the big pharmaceutical companies.

(Applause.)

DR. THROCKMORTON: Thank you. Sama Bellomo.

(No response.)

DR. THROCKMORTON: Kevin Zacharoff.

DR. ZACHAROFF: Hi. And before I say

anything more, I would just like you all to repeat in your minds what you heard Drs. Carr and Webster say, and put it in front of what I'm about to say, because I couldn't agree with what they said more.

I'm a lot of different things actually. I'm the vice president of a company up in Boston. We do research and develop technologies for healthcare solutions. I'm an anesthesiologist and pain medicine doctor, and I'm a teacher. I teach at the Stony Brook School of Medicine. From that perspective, I'd like us all, for the purposes of this meeting, to look up the definition of "efficacy," and to try to apply what we're going to talk about at this meeting, and apply it to the definition of efficacy, period.

With respect to the issues that we've heard a lot of people speak about, I'd like us to keep focused. And as hard as it is, we need to separate out efficacy from aberrant drug-related behavior. They're two different things. Maybe they occur in the same situation, but they're two different things.

We are currently working, in inflection, on an NIH-NIDA grant to actually develop the tool to measure outcomes and feed clinical effectiveness research; not only measuring negative outcomes, but also measuring positive outcomes.

Lastly, because I'm so yellow, I agree, the educational deficits are huge. I manage a website. We have 50,000 non-experts who subscribe to the website It's called painedu.org. It grows organically by a thousand people a month. It only scratches the surface. In the medical school I teach at, one day of four years of medical school is devoted to pain management. One hour of one day is devoted to opioids. Zero is devoted to aberrant drug-related behavior. Thank you.

(Applause.)

DR. THROCKMORTON: Thank you. Martin Levine.

(No response.)

DR. THROCKMORTON: Judy Rummler.

MS. RUMMLER: Thank you. My name is Judy Rummler. I'm the mother of Steve Rummler and

president of the Steve Rummler Memorial Foundation. I am here with Lexi Reed Holtum, our vice president and Steve's fiance. My husband Bill and I established the Steve Rummler Memorial Foundation after the death of our son Steve last July 1st. The mission our foundation is to heighten awareness of the dilemma of chronic pain and the disease of addiction and to improve the associated care process.

Steve's story is available on our website. It is a tragic part of the epidemic of prescription drug overdose deaths that is plaguing our country today. This epidemic has been fueled by the tremendous increase in prescriptions of opioids for pain. Steve was a wonderful, loving son. He was smart, and excelled in school and in sports. He was a gifted musician and a successful financial advisor. He loved his family. He was loved in return.

In 1996, Steve suffered a life-changing injury to his back. He suffered from chronic pain for 15 years. He sought help from many medical and

mental health professionals. He was prescribed antidepressants, benzodiazepines, and finally in 2005, opioids. And he told us how the opioids were helping his pain. By 2009, it became clear that Steve was getting prescriptions for his opioids from more than one doctor. With encouragement from his primary care doctor and his family, he decided to go to the Pain Rehabilitation Center at the Mayo Clinic in Rochester, Minnesota. He later went to the Hazelden Addiction Treatment Center in Center City, Minnesota.

Steve did not want to die and tried hard to fight the disease of addiction. Until the night of his death, he had never taken an opioid that had not been prescribed to him. We miss him terribly, and our lives will never be the same. I speak also for the many other families who have lost loved ones to this epidemic. The changes recommended by Dr. Kolodny are needed.

After Steve's death, we found a note among his belongings, referring to his treatment with opioid pain killers that said, "At first it was a

lifeline. Now it is a noose around my neck."

(Applause.)

DR. THROCKMORTON: Thank you. Lexi Reed.

MS. REED: Hi. Thanks for having me here today and listening to what I have to say. My name is Lexi Reed Holtum. Steve Rummler was my fiance. And Judy, his mother, is here with me today. I'm here because I want you to understand the destruction, waste and grief that prescription opioids cause in human lives in America today. And I assert that the FDA can do something about it, and should, today.

I'm asking you for help so that nobody else ever has to experience this needless loss again. Steve, before prescription opioids, was a multitalented, passionate, good man. He was generous, thoughtful, and compassionate. He worked hard and had a successful financial planning business, paid taxes, and was a socially responsible contributing member of society. He was loved and had a large community of friends and extended family, including myself and my 9-year-old

daughter, who loved him.

Steve's battle with prescription opioids was a brutal losing fight. He did not want to continue to be on them. Once he was on them, he lost all his passion. All intimacy was gone from our relationship. He became irresponsible and hurtful. He spent endless hours sleeping. And when he wasn't sleeping, most of the time he was unshaven, uncovered and nodding in and out of consciousness on our couch.

In the rare moments when he was conscious, he was desperately ashamed and remorseful of who he had become, what the opioids had done to him, and how he could not change. They literally hijacked his brain. Far from treating his pain and increasing his quality of life, prescription opioids ruined it. Steve didn't choose to die, and I believe that it is unethical for the FDA to continue to allow these prescription opioids to be handed out in the way in which they are. I believe that they need to take action now so that nobody else has to die. Steve did not need to die.

Please change the labeling now to Dr. Colony's recommendations. Thank you for your time.

(Applause.)

DR. THROCKMORTON: Thank you. Jan Chambers.

MS. CHAMBERS: Hello. My name is Jan Chambers. I'm the president of the National Fibromyalgia and Chronic Pain Association. Thank you for convening this workshop. And I'm very happy to be able to be here and represent over 6 million Americans who have fibromyalgia.

Fibromyalgia is a complex illness with complex symptoms. As Dr. Woolf stated earlier, only 25 percent of people in pain respond to the treatments that we have available. And physicians and patients are frustrated. Longitudinal studies are needed for the three recommendations that have been approved for fibromyalgia. We don't know what happens after 12 to 16 weeks. There needs to be much more research; not only funding, but a diversity of research.

The management of symptoms, including pain,

is very important to fibromyalgia patients, to the people that they love, their family units, and the people who care for them. We need at our disposal any and all reasonable methods of management associated with this disease. We have concerns around public policies related to access to care for our patient population. We encourage those in leadership positions to make decisions that are beneficial for the people with this painful illness.

The IOM report, Relieving Pain in America, made recommendations that federal agencies work together with other stakeholders, including patient advocacy organizations, to gather data, educate, and bring about a cultural transformation for chronic pain. That's what we're doing now. Steps in research have great promise for future beneficial treatment. We are seeking commitment from the FDA and from the NIH to see this through to the end. Opioid problems created attention and energy for serious dialogue on chronic pain illnesses. The end is to understand the cause and

create treatments for chronic pain illnesses.

The patient perspective on research, policy, and treatments is needed. Dr. Woolf indicated earlier that this is needed to help gain much more information from patients to understand what is happening in their central nervous systems. As a chronic pain patient, I know we are stuck. We are still stigmatized within the healthcare community, outside of this educated group of researchers.

Currently, the loss of control to manage our bodies often equates to a loss of dignity when we're trying to discuss with our physicians that it's not all in our heads; that we are not imagining all of these symptoms. We don't want a loss of grey matter in our brains. We don't want to have continued problems. But we don't have many options, and we need your help to become unstuck through increased funding, research, translational research, and educating others that fibromyalgia is a central nervous system disease.

Thank you very much for your attention. And please let us know how we can help you, how we can

be of assistance to have reasonable access to care, contribute to better policies, and to facilitate research. Thank you.

(Applause.)

DR. THROCKMORTON: Thank you. Robert Mitchell.

DR. MITCHELL: Yes. I'm calling in by phone. Can you hear me?

DR. THROCKMORTON: Yes, we can.

DR. MITCHELL: My name is Robert Mitchell, and I am an osteopathic physician in North Miami Beach, Florida. Since this symposium is addressing non-pharmacological strategies as adjuncts to pain management, I would like to talk about the responsibility of state medical boards to oversee physicians they license. In Florida, the MD medical board and the osteopathic medical board are both part of the Department of Health, whose mission is to promote and protect the health of all residents and visitors in Florida.

Because of five deaths in 1999 from surgery performed in doctors' offices, Florida's MD medical

board issued three state-wide emergency orders that restricted office-based surgery until new safety guidelines could be implemented. By tacit proxy, Florida's osteopathic physicians were also bound by these orders because they dramatically altered the standard of medical care.

In comparison, during the pain management pill-mill massacres that have ravaged our state for over 10 years now, neither the MD nor the osteopathic medical boards in Florida have issued one single state-wide emergency order to end this tragedy, even though thousands of prescribed opioid overdose deaths have been documented online each year by the Florida Department of Law Enforcement.

A 2009 grand jury investigation into the proliferation of pain clinics in South Florida stated that whether the boards of medicine will have the fortitude to regulate and discipline its members in this very lucrative field is another question. In other words, in Florida, money is more important than patients' safety. In medicine, medical boards provide the ultimate oversight for

patient care and welfare. So let us not forget that it's the person shooting the gun who kills. It's the doctor who knowingly and improperly writes pain pills that murder. And it's the medical board that fails to take all necessary and reasonable precautions that sets the stage for disaster.

Thank you. And anyone wanting to contact me, I'm at 786-262-5750. Thank you very much.

DR. THROCKMORTON: Thank you very much.

(Applause.)

Closing Remarks – Douglas Throckmorton

DR. THROCKMORTON: Mary, I think with that, that's the end of the open public hearing. I'm going to keep my remarks very brief in the interest of time.

Let me just say, first off, thank you to everyone that's participated in the sessions that we've had so far today and looking forward to tomorrow. The FDA is listening very carefully to the things that we're hearing, both from the scientists and from everyone else who's speaking.

In particular, let me thank the speakers in

the open public hearing. The passion that you all have, from whatever perspective you're coming, illustrates how really challenging this is, how terribly important it is we get this right, and that we really do need all of your help. We need all of the help that we can find, both within the communities you service as well as the academic communities that we look to for scientific input.

Thank you very much, and I look forward to continue the discussions tomorrow morning.

(Applause.)

(Whereupon, at 5:27 p.m., the meeting was concluded.)