

1 FOOD AND DRUG ADMINISTRATION
2 CENTER FOR DRUG EVALUATION AND RESEARCH
3
4

5 ASSESSMENT OF ANALGESIC TREATMENT OF
6 CHRONIC PAIN: A SCIENTIFIC WORKSHOP
7
8

9 Wednesday, May 30, 2012

10 1:00 p.m. to 5:30 p.m.
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15 Natcher Auditorium
16 Natcher Conference Center
17 NIH Campus
18 45 Center Drive
19 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

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

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

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

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

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

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

1 interventions.

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

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

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

1 audience.

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

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

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

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

6 Please do not speak unless you are
7 recognized by Dr. Throckmorton, me, or the
8 moderator for a particular panel. We will do our
9 best to allow ample time for questions from the
10 audience according to the agenda. If you are
11 recognized, please use your limited time
12 efficiently, and if asked to yield the floor to the
13 next person waiting to ask a question, please do
14 so.

15 Finally, and perhaps most
16 importantly, while there are clearly strong
17 opinions and powerful emotions tied to the issues
18 under discussion, we can only have a successful
19 workshop if everyone in this room treats each other
20 with the respect and courtesy that we are all due.
21 Please allow people to have their say without
22 expression of disagreement during that time. We'll
do our best to assure that all points of view are

1 considered and as many voices as possible are
2 heard.

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

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

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

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

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

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

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

5 **Moderator - David Thomas**

6 DR. THOMAS: Thanks, Bob.

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

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

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

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

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

1 Dr. Woolf.

2 (Applause.)

3 **Presentation - Clifford Woolf**

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

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

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

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

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

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

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

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

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

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

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

18 So the responder rate is currently -- with
19 the available treatment, the best available
20 treatment, the gold standard treatment -- is about
21 25 percent, which means that 75 percent of patients
22 are getting treatment and are not responding to it.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Why is this important? Because once we

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

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

22 Here is another example. Here is

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

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

1 spontaneous pain-like sensations in the patient.

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

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

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

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

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

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

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

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

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

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

22 Again, if we can identify patients where

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

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

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

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

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

22 Well, the answer is that we need indirect

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

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

1 German neuropathic pain network and Ralf Baron.

2 And these are measurements that they routinely make
3 in the large patient cohort they have collected.

4 Then we have positive symptoms, evoked pain.

5 So these are spontaneous pains, and these are
6 evoked pains. And these include mechanical dynamic
7 allodynia, pain in response to the light touch;
8 static allodynia; hyperalgesia, which is pain in
9 response to a noxious stimulus; temporal summation
10 of pain, et cetera. The point is that
11 collectively, if measured in a systematic way in
12 our patients, they can provide a fingerprint, a
13 pain fingerprint, that may uniquely reflect what is
14 going on in that patient's nervous system to
15 generate the pain.

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

1 only has a small element of it.

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

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

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

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

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

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

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

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

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

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

7 Thank you.

8 (Applause.)

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

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

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

1 numerous grants from the NIH and has published more
2 than 150 articles and book chapters, and has edited
3 three books and authored one. He has received
4 numerous awards, including the University of
5 Florida Research Foundation Professorship and the
6 2009 Wilbert Fordyce Clinical Investigator Award
7 from the American Pain Society.

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

11 Roger.

12 **Presentation - Roger Fillingim**

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

20 Here is a disclosure.

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

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

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

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

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

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

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

1 and on to physiological responses.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 And I thank you for your attention.

2 (Applause.)

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

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

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

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

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

4 Bill.

5 **Presentation - William Maixner**

6 DR. MAIXNER: Thank you, David.

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

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

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

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

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

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

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

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

1 chronic pain.

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

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

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

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

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

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

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

22 The first vignette I'm going to show is a

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

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

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

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

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

1 these other two types of genetic polymorphisms.

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

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

1 showed very low levels of sensitivity.

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

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

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

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

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

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

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

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

1 significant patient preference for the propranolol
2 arm.

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

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

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

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

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

1 the future.

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

7 (Applause.)

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

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

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

4 The title of his talk is Neuroimaging
5 Biomarkers for Pain.

6 Sean.

7 **Presentation - Sean Mackey**

8 DR. MACKEY: Thank you.

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

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

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

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

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

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

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

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

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

10 This is a study that was done several years
11 ago by Kim, et al. They gave a 49-degree Celsius
12 stimulus; found that people reported it anywhere
13 from zero out of 100, all the way up to 100 out of
14 100 and everything in between; identify that there
15 are significant sex-related factors here, ethnic
16 factors. Genetic factors play a role. But also
17 anxiety, catastrophizing, somatization, personality
18 characteristics also playing a role, which by the
19 very nature defines this as a brain-related
20 phenomenon.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 healthy volunteers.

2 Napadow and his group followed up with
3 this -- looking at patients with fibromyalgia, a
4 condition that afflicts 4 to 6 million Americans,
5 80 percent of them women, terrible, terrible pain.
6 It takes a huge toll on their life -- and found
7 that if you can compare them against healthy
8 controls, what you find is in looking at
9 networking, network connectivity of this default
10 mode network with some of the sensorimotor areas,
11 you find abnormal connectivity; that there are
12 abnormal connections in these networks to other
13 regions that are involved with bodily awareness and
14 sensory function, showing, once again, that chronic
15 pain is associated with fundamental alterations in
16 the way information is flowing within our brain.

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

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

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

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

1 thinning, and there was actual thickening of that.

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

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

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

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

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

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

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

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

1 ultimately use brain imaging to get us there.

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

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

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

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

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

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

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

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

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

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

13 (Laughter.)

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

17 **Questions and Answers**

18 DR. THOMAS: Thank you, Sean.

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

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

1 affiliation.

2 (Pause.)

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

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

7 DR. MAIXNER: Yes.

8 (Laughter.)

9 DR. THOMAS: Okay. How about you.

10 DR. VON KORFF: Mike Von Korff from Seattle.

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

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

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

1 structural changes represent. Do they represent
2 changes in dendritic sprouting? Do they represent
3 actual changes in neuronal cell density? Do they
4 represent changes in fluid? Do they represent
5 changes in glia?

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

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

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

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

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

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

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

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

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

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

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

22 DR. MAIXNER: And just one other comment,

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

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

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

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

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

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

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

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

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

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

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

22 We've tended to study them independently,

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

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

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

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

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

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

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

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

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

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

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

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

18 DR. THOMAS: Thank you, Sean.

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

1 in thanking our speakers.

2 (Applause.)

3 (Whereupon, a recess was taken.)

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

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

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

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

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

10 (Applause.)

11 **Moderator - Len Paulozzi**

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

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

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

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

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

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

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

10 Dr. Stewart.

11 **Presentation - Walter Stewart**

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

16 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

1 and then other pain that arises from diseases or
2 events.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 With regard to age, it really varies

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

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

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

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

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

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

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

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

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

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

8 I mentioned earlier that migraine and other
9 pain disorders are inversely related to
10 socioeconomic status. On this axis here is the
11 prevalence ratio, where the lowest income group is
12 1 and the others are relative to that. And you see
13 the same gradient. This is for migraine, the
14 prevalence ratio of migraine in relation to income,
15 and a very sort of strong relationship.

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

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

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

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

1 higher income groups.

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

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

22 In this graph, I show the inverse

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

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

1 whether it remits or translates into a progressive
2 disorder.

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

17 If you look among those who are employed and
18 the most common pain disorders, the most common
19 episodic pain disorders, they account for more than
20 \$60 billion in overall costs. But this represents
21 only a share of the overall costs because we know
22 that as the frequency of episodes of pain goes up,

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

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

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

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

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

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

17 So I'll stop there.

18 (Applause.)

19 DR. PAULOZZI: Thank you, Dr. Stewart.

20 Our next speaker is Dr. Michael Von Korff.

21 Dr. Von Korff is a senior investigator at the Group
22 Health Research Institute, Group Health

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

13 Dr. Von Korff.

14 **Presentation - Michael Von Korff**

15 DR. VON KORFF: Thanks a lot, Len.

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

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

1 long-term chronic opioid therapy in particular.

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

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

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

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

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

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

1 between 1995 and 2005. More recent drug
2 enforcement data has shown the per capita retail
3 sales of opioids have continued to increase through
4 2010.

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

16 Analyses of U.S. mortality data by Len
17 Paulozzi's group at CDC has shown that the rate of
18 fatal drug overdose involving prescription opioids
19 increased fourfold from 1999 through 2009.

20 Analyses of drug treatment data by the Substance
21 Abuse and Mental Health Service Administration has
22 shown that the admission rate for treatment of

1 prescription opioid addiction also increased
2 fourfold from 1999 to 2009.

3 It's unusual to detect adverse health
4 effects of prescription drug changes and
5 prescribing of prescription drugs with national
6 surveillance data. So as Bob Rappaport indicated
7 at the beginning of this meeting, this is something
8 that needs to be taken very seriously.

9 Understanding these trends from aggregate
10 ecological data requires more refined analyses
11 directly relating drug exposures to potential
12 adverse outcomes.

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

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

4 Unfortunately, epidemiologic research on
5 morbidity and mortality risks related to opioids
6 has not kept pace with changes in community
7 practice that have occurred over the last 15 to
8 20 years, so epidemiologists are now playing
9 catch-up in studying health risks related to
10 long-term opioid use. This is important because
11 experience with opioids in the context of acute
12 use -- and there's substantial experience, clinical
13 experience and experimental experience -- that
14 experience with acute use does not adequately
15 inform the effectiveness and safety of long-term
16 opioid use.

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

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

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

22 So it's informative to compare where we

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

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

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

22 Gaps in knowledge concerning the

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

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

19 In 2009, we completed the largest survey to
20 date of a representative sample of a little over
21 2100 chronic opioid therapy patients being treated
22 in primary care settings from two large health

1 plans. We have been using these data to understand
2 how chronic opioid therapy patients in community
3 practice use opioid medications, how they are doing
4 in terms of pain and function, and how patients
5 perceive opioids as a treatment for chronic pain.
6 The large majority of patients in these settings
7 were using average daily doses of less than
8 50 milligrams morphine equivalents, while a smaller
9 percentage received doses of 120 milligrams or
10 more.

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

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

1 scale. As you might expect, we found substantial
2 variation in pain ratings for chronic opioid
3 therapy patients at each dosage level. So this
4 variation of the responses, this is what you were
5 hearing about this morning. This is to be
6 expected. But this also has important clinical
7 relevance when you start thinking about what we
8 should be doing, how we should be managing opioids
9 in the community. Overall, about one-half of the
10 chronic opioid therapy patients rated their pain
11 intensity in the moderate range. About one-third
12 rated their pain the severe range. And about 1 in
13 10 rated their pain in the mild range.

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

1 higher dose regimen.

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

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

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

1 dose.

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

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

1 5 percent reported non-medical use of OxyContin in
2 the prior year.

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

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

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

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

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

1 dose regimens.

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

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

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

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

4 Thank you very much for your attention.

5 (Applause.)

6 **Questions and Answers**

7 DR. PAULOZZI: Thank you to most of our
8 speakers for some excellent reviews. We have now
9 10 minutes for questions, and we'll sit up here.

10 If folks could line up at the micas.

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

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

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

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

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

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

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

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

9 DR. STEWART: Are you an epidemiologist?

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

12 (Laughter and applause.)

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

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

1 assume that it depends. If the average visit is
2 3.2 minutes to a physician, I don't know that
3 everybody asks those history questions.

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

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

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

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

7 DR. DUDA: My name's Lawrence Duda. I'm a
8 general dentist from Albany, New York. I've been
9 in practice for 40 years. I noticed the graph. In
10 1998, the percentage of opioids take off as far as
11 the prescriptions, the amount of pills out there.

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

22 DR. PAULOZZI: Yes. I could comment on

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

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

18 Go ahead. Next question.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

16 DR. CHAUMONT: The question is, should we be
17 inducing family practitioners to prescribe
18 160 milligram dosing of OxyContin in a primary care
19 setting, having pictures of patients, photographs
20 of patients -- they're smiling. This one is for
21 5 milligram, and this is for 80 milligram
22 twice-a-day dosing. Should those recommendations

1 be liberally made in view of the present
2 recommendations?

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

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

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

22 DR. PAULOZZI: Okay. Thank you very much.

1 This concludes the session. Thanks again to our
2 speakers.

3 (Applause.)

4 **Open Public Hearing**

5 DR. THROCKMORTON: Thanks, Len, very much.

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

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

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

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

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

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

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

19 (Pause.)

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

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

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

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

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

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

1 and isolated.

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

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

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

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

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

19 (Applause.)

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

22 DR. KOLODNY: My name is Andrew Kolodny.

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

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

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

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

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

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

15 DR. THROCKMORTON: Thank you.

16 (Applause.)

17 DR. THROCKMORTON: Pete Jackson, also from
18 PROP.

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

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

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

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

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

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

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

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

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

21 (Applause.)

22 DR. THROCKMORTON: Thank you, Pete.

1 Daniel Carr, from the American Society of
2 Anesthesiologists.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 outcomes data on treatment effectiveness in
2 everyday settings of care.

3 Thank you.

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

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

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

1 of those who would abuse and divert them?

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

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

1 withdrawal.

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

13 DR. THROCKMORTON: Thank you.

14 (Applause.)

15 DR. THROCKMORTON: Betts Tully.

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

1 effects.

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

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

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

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

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

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

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

22 I am a chronic pain patient. I understand

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

6 DR. THROCKMORTON: Thank you.

7 (Applause.)

8 DR. THROCKMORTON: Kathleen Zinno.

9 (No response.)

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

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

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

1 years later, the State of New York, utilizing their
2 professional assistance program, asked me to stop
3 using drugs and enter into recovery, and I did.

4 After a few months of treatment and a
5 life-threatening seizure, one week in the hospital,
6 the PAP, the Professional Assistance Program, said
7 I could restart my dental practice, and I did. I
8 have never been addicted since. Sixteen years of
9 my life has been restored and never better.

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

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

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

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

10
11 (Applause.)

12 DR. THROCKMORTON: Thank you. Jorge
13 Chaumont.

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

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

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

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

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

1 convincing to warrant their use.

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

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

1 Thank you for your time.

2 (Applause.)

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

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

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

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

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

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

15 (Applause.)

16 DR. THROCKMORTON: Thank you. Lynn Webster.

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

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

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

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

22 Pain is multidimensional, and people respond

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

10 Thank you very much.

11 (Applause.)

12 DR. THROCKMORTON: Thank you. Colonel
13 Walter Craig.

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

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

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

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

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

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

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

10 DR. THROCKMORTON: Thank you.

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

19 More to the point, the prudent use of Kadian
20 and oxycodone opioids have been a lifesaver to me,
21 100 milligrams of Kadian a day, 20 to 40 milligrams
22 of oxycodone a day. Now, however, the use of

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

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

1 as an unintended consequence of ill-founded
2 actions.

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

10 (Applause.)

11 DR. THROCKMORTON: Thank you. Harris
12 Silver.

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

22 A year later, I had a revision surgery on my

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

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

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

22 Despite being terrified of tapering off the

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

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

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

20 (Applause.)

21 DR. THROCKMORTON: Thank you. Mark Odden.

22 MR. ODDEN: Good afternoon. My name is Mark

1 Odden. I'm a certified registered nurse
2 anesthetist, who's rural Iowa anesthesia practice
3 includes pain management services. I am pleased to
4 represent and speak on behalf of the American
5 Association of Nurse Anesthetists, which represents
6 44,000 CRNAs and student nurse anesthetists who
7 deliver more than 32 million anesthetics in the
8 United States each year. Pain management is a
9 critical aspect of the anesthesia care continuum
10 providing acute and chronic pain management
11 services, and this is within the CRNA's
12 professional scope of practice.

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

1 pain states.

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

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

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

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

17 (Applause.)

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

20 (No response.)

21 DR. THROCKMORTON: Larry Golbom.

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

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

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

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

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

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

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

14 DR. THROCKMORTON: Thank you. Shani Weber.

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

17 DR. THROCKMORTON: Apologies.

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

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

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

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

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

1 had.

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

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

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

1 (Applause.)

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

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

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

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

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

22 Like others, I am determined to keep my life

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

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

20 Thank you for this opportunity.

21 (Applause.)

22 DR. THROCKMORTON: Thank you. Melody

1 Meginity. I may have that wrong, too.

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

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

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

1 society.

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

13 (Applause.)

14 DR. THROCKMORTON: Thank you.

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

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

1 (No response.)

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

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

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

18 (Hands raised.)

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

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

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

18 (Applause.)

19 DR. THROCKMORTON: Thank you. Sama Bellomo.

20 (No response.)

21 DR. THROCKMORTON: Kevin Zacharoff.

22 DR. ZACHAROFF: Hi. And before I say

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

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

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

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

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

16 (Applause.)

17 DR. THROCKMORTON: Thank you. Martin
18 Levine.

19 (No response.)

20 DR. THROCKMORTON: Judy Rummler.

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

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

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

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

1 mental health professionals. He was prescribed
2 antidepressants, benzodiazepines, and finally in
3 2005, opioids. And he told us how the opioids were
4 helping his pain. By 2009, it became clear that
5 Steve was getting prescriptions for his opioids
6 from more than one doctor. With encouragement from
7 his primary care doctor and his family, he decided
8 to go to the Pain Rehabilitation Center at the Mayo
9 Clinic in Rochester, Minnesota. He later went to
10 the Hazelden Addiction Treatment Center in Center
11 City, Minnesota.

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

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

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

2 (Applause.)

3 DR. THROCKMORTON: Thank you. Lexi Reed.

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

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

1 daughter, who loved him.

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

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

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

4 (Applause.)

5 DR. THROCKMORTON: Thank you. Jan Chambers.

6 MS. CHAMBERS: Hello. My name is Jan
7 Chambers. I'm the president of the National
8 Fibromyalgia and Chronic Pain Association. Thank
9 you for convening this workshop. And I'm very
10 happy to be able to be here and represent over
11 6 million Americans who have fibromyalgia.

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

22 The management of symptoms, including pain,

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

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

1 create treatments for chronic pain illnesses.

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

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

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

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

4 (Applause.)

5 DR. THROCKMORTON: Thank you. Robert
6 Mitchell.

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

9 DR. THROCKMORTON: Yes, we can.

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

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

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

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

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

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

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

9 DR. THROCKMORTON: Thank you very much.

10 (Applause.)

11 **Closing Remarks - Douglas Throckmorton**

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

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

22 In particular, let me thank the speakers in

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

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

11 (Applause.)

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