FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# ASSESSMENT OF ANALGESIC TREATMENT OF CHRONIC PAIN: A SCIENTIFIC WORKSHOP

Thursday, May 31, 2012

8:30 a.m. to 4:45 p.m.

Natcher Auditorium

Natcher Conference Center

NIH Campus

45 Center Drive

Bethesda, Maryland 20892

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:36 a.m.)

DR. THROCKMORTON: Good morning, everyone. If you could take your seats, I think we're going to begin the second day of this meeting.

I'm going to begin just by saying, first, thank you for yesterday's conversations. I look forward to the discussions today, which are going to form a lot of the things that will help us set an agenda for next steps.

Our first speaker this morning is going to be Dr. Janet Woodcock, who's the center director for the Center for Drug Evaluation and Research. She's also a rheumatologist and has also been someone that has been very supportive, very interested in the issues around the treatment of pain, the treatment of patients with pain. And she's going to give us some introductory remarks.

Janet? Thank you.

**Opening Remarks**

DR. WOODCOCK: Thanks, Doug, and good morning, everyone. I'm delighted to be here and

that this workshop is going on.

We're having this meeting because of a set of dilemmas that affect our whole country and, in fact, around the world, and that is that there is a large number of people, of course, with inadequately treated pain that our current modalities really don't address very well.

On the other hand, our current modalities have significant liabilities, all of them, almost. And the liability that you're particularly addressing today is the fact that the prescription opioids have become a major source of drug abuse and addiction in the United States, as we all know. And there's an epidemic of that problem.

So to go through these two issues in more detail, prescription opioid abuse or misuse has really become a major public health problem in the U.S., surpassing almost illegal drug abuse. There are many people, of course, including the current administration, that are trying to address this problem with a lot of risk mitigation strategies and various interventions.

The FDA is doing some formal REMS interventions on certain opioids; that's our risk evaluation and mitigation strategy. And one thing that has been suggested repeatedly is that we should limit the indications for potent opioid analgesics to acute pain and to chronic pain only for cancer, which is usually a kind of progressive pain.

Advocates for this change in how the products would be indicated and marketed point to the fact there's a lack of data demonstrating the efficacy of opioids for chronic non-cancer pain.

Now, typically, for FDA, there's a large evidence base, a significant body of peer-reviewed and FDA-reviewed medical literature demonstrating efficacy of potent opioids for up to 12 weeks of treatment. So that evidence base is strong and secure that these products work in that window of time.

But their performance after 12 weeks and how their liabilities -- for example, increased tolerance, increased dependence, and so

forth -- how this progresses past that time is less clear, and not demonstrated in the type of evidentiary base that FDA usually has for approval for when we grant an indication. So that makes it difficult for the FDA to determine what type of instructions might be given in the drug labels, and thus to limit marketing and so forth.

Then there's also felt to be a public health crisis on the other hand about the inadequate treatment of pain, and this issue continues. This was brought up a lot, of course, during the year of pain or the decade of pain or whatever, a while ago. But currently, we still have this problem in the United States, and there is a recent IOM report called, Relieving Pain in America, that talks about the number -- over 100 million adults in the United States have a chronic pain condition that cost over $500 billion annually in direct medical costs and lost productivity.

So clearly, pain or pain syndromes -- but these are writ large; these are a wide variety of types of syndromes -- are a major morbidity

affecting the population and resulting in not only suffering but inability to work and inability to function.

So these IOM authors concluded that there is currently a crisis in treatment of pain in the United States. But before we decide if we want to reposition the opioids and their indications, we have to look at the data, and we have to have an evidentiary base for any changes that we would make.

We can take steps on the opioids that then cause other problems, both for the population and for the medical community. We could exacerbate the problem of inadequately treated pain, of course, and that's one of the concerns that we have and the community has.

In fact, we don't have any really good modalities for treatment of pain. And probably the opioids are one of the best modalities for acute pain, but most of the modalities that we use have significant liabilities. And each one of those, each type of pain -- at least for drugs,

medicines -- we have been urged to remove from the market. All of them, all right, for various reasons.

So if you're a treating clinician, and I'm sure you have been discussing this at this meeting, you're not faced with a wide variety of highly effective and highly safe -- in other words, not having any severe liability -- modalities that you can use.

I think part of this is that in the treatment of chronic pain, most of the modalities we currently have don't address the underlying generation of the pain or the pathophysiology that leads the pain or symptomatic control. And so I think more research is needed, especially in chronic pain, on the origin of that pain and diagnosis of what type of pathophysiology is going on so that more targeted interventions can be used.

But the question whether opioid analgesics are effective in chronic non-cancer pain cannot be addressed without looking at the efficacy of the other analgesic drug products that could be used to

treat chronic pain or other modalities. So we have to look at this in the context of the treatments that we have.

So within the focus -- well, the focus of this meeting is on use of opioids. The larger question of use of analgesics for pain is highly relevant, and we would like to have comments during the meeting on this topic because if one modality is removed or diminished, then something else would need to be used.

In general, we think that one result that would be a very important outcome for this day of the workshop would be the development of a research agenda. And this agenda would have multiple components, one, to better understand how to use analgesic drugs overall, and opioid analgesics in particular. And I think some of the basic science questions that are pertinent to this have already been raised yesterday.

Second, we need to understand how to mitigate, particularly for opioids, the risks of abuse, addiction, and overdose. And research on

these topics would be extremely important, so what we need to do is define what we know so that we understand what we don't know, and then try to develop a research agenda to fill in those gaps.

Then to define which, if any, specific patient populations where the opioid analgesics actually do provide effective analgesia for long-term use. And I gather you heard from a lot of patient groups yesterday about their need for various interventions to deal with their pain and suffering. And the question is what intervention would be appropriate in which group? I think that research agenda is broad, and particularly with opioids. Are there specific groups where this is the most appropriate intervention out of the current armamentarium or future interventions we could think of?

So there is a lot of controversy in this whole area, and this scientific workshop is intended to bring the facts to the table in a public forum so we can talk about what we know, what we don't know, and what research is needed to

fill in the gaps on a proper use of opioids and other analgesics in chronic pain.

So hopefully, I think the research agenda that is created today will find the necessary support. If as part of these deliberations and presentations you can lay out the issues and what research needs to be done in these various areas, our job, I think, at the FDA is to seek mechanisms so that this research could go forward: consortia or use of other stakeholders working with the pharmaceutical industry, the academic community, NIH, and of course, the private, nonprofit sector to see if we can't get the research done.

So if such an agenda can be established, and we can understand the broad outlines of what information needs to be generated, we can commit that we will try to move it forward quickly so that we can ultimately provide better treatment for the millions of Americans who suffer from chronic pain, and at the same time protect them and other members of the community from some of the devastating consequences of abuse and addiction. Thank you.

(Applause.)

DR. RAPPAPORT: Thank you so much, Dr. Woodcock. As I mentioned yesterday, Drs. Woodcock and Throckmorton have really been an incredible support for making this workshop happen, and it's one that's been needed for a long time.

I have the great pleasure of introducing our first moderator today, Dr. Robert Dworkin. Dr. Dworkin is a professor of anesthesiology, neurology, oncology, and psychiatry at the University of Rochester Medical Center. He's a leading international expert in pain, in particular in neuropathic pain. He's one of the world's experts on clinical trials in pain.

I've been fortunate to work with him on the Impact initiative on clinical trials in analgesia, with Bob and his colleague who have been leading Impact for over a decade now, Dennis Turk from the University of Washington. And I'm also very pleased that Bob is the primary investigator in our partnership under ACTION at University of Rochester.

So I've known him very well. I think he's an outstanding moderator in the situations I've seen him in. And I think he's going to have a bit of a challenge today, but I think he's up to the challenge.

This is a key session this panel, because, really, this is the session on what does the data show. And at the end of this period, I think we'll all hopefully have a better idea of what we really -- as Janet just said, what we really do know, what we don't know, and what the research agenda should be. So Bob?

**Panel 3 - Robert Dworkin - Moderator**

DR. DWORKIN: Thanks very much, Bob. I really appreciate your comments, and I hope I do a good job.

The objective of this morning's session is to review and discuss the evidence for the efficacy and effectiveness of opioid analgesics and other treatments for patients with chronic non-cancer pain. And we are very fortunate to have a very distinguished group of individuals as presenters

and as panelists.

The individuals who you'll be hearing from this morning have made fundamental contributions to our understanding of the neurobiologic, and psychosocial mechanisms of chronic pain, and also to the identification of efficacious treatments for patients with a variety of chronic pain conditions.

They have received multiple awards, served in major leadership positions in multiple professional societies, and have authored numerous publications. I thought last night of doing a Google search and coming up with the total number of publications of our panelists and presenters. I didn't have time for it, but it would be close to 2,000.

So therefore, in the interest of leaving as much time as possible for discussion this morning, I will mention only one or two especially noteworthy accomplishments when introducing each of our speakers rather than describing their impressive achievements in detail, though I will say a little bit about each of them.

So before we get going, just a couple of housekeeping kinds of things. I've been asked to remind you all that disclosures of potential conflicts of interest for all the speakers and panelists are available online at the meeting website.

Then, finally, I would like to really beg our speakers and panelists to please adhere to the 20 minutes that they've been allotted if they are presenters, and the 5 minutes they've been allotted if they are panelists.

We really would like to leave as much time as possible for discussion, as you can see from the agenda, among the panelists and presenters, and then also, importantly, with all of you in the audience.

So it's really my great pleasure to introduce our first speaker, Dr. Srinivasa Raja. Raj is a professor of anesthesiology and critical care medicine, and a professor of neurology, at Johns Hopkins School of Medicine.

He's currently president-elect of the

Neuropathic Pain Special Interest Group of the International Association for the Study of Pain -- that's IASP; many of you here are members of that. He's also chair of the Scientific Committee for the upcoming 2014 World Congress of IASP.

As is also true of all of our other speakers and panelists, there are a lot of other achievements. But right now, we would like to hear what he has to say about the evidence for the efficacy of opioid analgesics for chronic pain patients from randomized clinical trials.

**Presentation – Srinivasa Raja**

DR. RAJA: Thank you, Bob.

Good morning, ladies and gentlemen. I've been given this uphill task by the two Bobs, Drs. Dworkin and Rappaport, to summarize the data based on randomized, controlled trials on the efficacy of opioids for chronic non-cancer pain in the next 20 minutes.

So the path I will take is to first give you an overview of the clinical models used, the drugs

studied, the designs, and the outcome measures, before providing you with the results of some of these studies.

Clinically, chronic pain states have been described as nociceptive or inflammatory and neuropathic, examples of the former being chronic osteoarthritis and the latter being postherpetic neuralgia or diabetic neuropathic pain. In some pain states, such as cancer pain, these two types of pain may coexist.

Neither group of chronic pain states that have been described -- are these dysfunctional pain states or central sensitization syndromes exemplified by fibromyalgia or irritable bowel syndromes.

So what I hope to do in the available time is to concentrate and focus on the evidence from peer-reviewed publications of randomized, controlled trials on neuropathic and nociceptive pain states, and use meta-analysis and critical reviews of the literature to summarize the data from some of these studies.

What I will not be able to discuss are trials in cancer and dysfunctional pain states, the role of opioids based on controlled trials for breakthrough pain, or the adverse effects associated with the use of opioids.

So the clinical models that have been used for chronic nociceptive pain have been predominately osteoarthritis and low back pain. In contrast, for the chronic neuropathic pain states, most of the models used clinically to study the efficacy of opioids have been postherpetic neuralgia or diabetic neuropathic pain.

The inclusion criteria in the majority of these studies have been adults who have been rated at 4 or greater in a zero to 10 scale, or pain of moderate or severe intensity that has not been adequately controlled with NSAIDs or COX-2 inhibitors.

A number of study designs have been used. The majority of the studies for FDA approval of drugs have used the parallel double-blind comparisons. Some studies from academic

institutions or single-center studies have used a crossover type of design, and more recently, an enriched enrollment design, where the active drug is compared with a placebo and/or an active comparator. And I'll provide a little bit more discussion on this in the next slide.

As has already been described, the majority of these studies have examined the efficacy of opioids over a 4- to 12-week randomized period.

So in the enriched enrollment design, the usual strategy is to screen patients using a run-in period, which is an open label period. And predominately, this run-in period is to determine eligible patients based on either treatment response and/or tolerability of the drug so that they can subsequently be re-randomized to an active drug or a placebo.

In some studies, an additional group has been added as an active comparator, mainly as an assay sensitivity and, in a few cases, to examine for lack of inferiority.

The opioids studied in most of these

randomized, controlled trials have been mu-opioid agonists, predominately. However, some drugs, such as mu-agonists, which have an additional effect of reuptake inhibition of catechol such as norepinephrine and serotonin, also been included, example being tramadol.

A mu-opioid agonist for the selective norepinephrine reuptake inhibition is exemplified by tapentadol. Buprenorphine is an opioid agonist which, in addition to mu-agonist effects, may have agonist effects on the kappa and delta receptors.

The primary outcome measures in the majority of these randomized, controlled trials have been pain intensity, with subsequent analysis of responder rates or number needed to treat for 30 percent or 50 percent response rates. Other secondary outcome measures have included pain relief, global outcome impressions of change, quality of sleep, physical function, and quality of life, but these have been predominantly secondary outcome measures.

As far as the primary outcome measure, pain

intensity, is concerned, the scales commonly used are the numerical rating scale, 5-point categorical scales, a VAS scale of zero to 100, or the WOMAC osteoarthritis index scales.

So let's move on to evidence from trials. I'll start with some trials on nociceptive pain states. One of the early trials was on oral morphine for soft tissue and musculoskeletal pain using a double-blind, two-period crossover design with a three-week titration and a six-week maintenance done by Dwight Moulin from Canada.

Based on the response to morphine, which was the opioid used in this case, controlled-release morphine, 60 milligrams twice a day, the authors concluded that in patients with treatment-resistant chronic regional pain of soft tissue of musculoskeletal origin, oral morphine in doses up to 120 milligrams per day may confer analgesic benefit. This was one of the early studies done, almost 15 years ago.

A more recent study examined oxymorphone extended-release in chronic low back pain. The

design here is one of those enriched enrollment designs, where starting from eligible patients of 325 patients, 205 patients were chosen based on their tolerability and efficacy of oxymorphone. These patients were then randomized to either placebo therapy or treatment with oxymorphone extended-release, and over a 12-week double-blind period.

So over this period, one can see that the placebo group, the pain intensity increased, which was significantly different from the opioid-treated group. And at the end of the 12-week therapy, more than 50 percent of patients in the placebo-treated group dropped out due to lack of efficacy, while a significantly smaller proportion of patients in the opioid-treated group dropped out.

Another study in chronic low back pain included transdermal buprenorphine, which was again a similar enriched enrollment trial with a comparator group here. Here again, from nearly 1200 patients, 660 patients were chosen based on their analgesia and tolerability to a buprenorphine

transdermal application of 20 micrograms per hour.

These 660 patients were then randomized in a double-blind fashion and followed for 12 weeks, into either a low-dose buprenorphine, 5-micrograms-per-hour patch or a 20-micrograms-per-hour patch, or oxycodone immediate release, 40 milligrams per day.

The outcome measure here was the mean difference from the low-dose transdermal buprenorphine, the 5 micrograms per hour, over the 4-, 8-, and 12-week period. And the data showed that the transdermal buprenorphine, 20 micrograms per hour and the oxycodone immediate release, 40 milligrams per day, had a greater reduction in pain intensity compared to the lower dose, and the difference scores were about .67 and .75 in the zero to 10 scale, so a moderate effect.

The other common model of nociceptive pain states has been chronic osteoarthritis of the knee or hip. And in this study with tapentadol extended-release, an active and a placebo-controlled parallel study was designed, again a 12-

week maintenance period, where subjects were treated with either a placebo therapy or an extended-release tapentadol for the 12-week period.

A third group, extended-release oxycodone, was used primarily for assay analysis, and the observations were that compared to baseline, the average pain throughout the maintenance period was reduced both in the extended-release tapentadol group as well as the oxycodone controlled-release group.

A Cochrane review of all the studies on -- more than 10 studies, which included over 2,000 patients, using oral or transdermal opioids for osteoarthritis of the knee or hip shows that the reduction in pain intensity with opioids was greater compared to that with placebo across these trials. In addition, there was a moderate improvement in function based on the WOMAC scale as well.

What they did observe was that there was no substantial difference in the efficacy of opioids, depending on the type of opioid used, the potency

of the opioids, whether it was a weak or a strong opioid, the trial methodology, or the type of funding that funded the study.

So based on this Cochrane review of the 10 trials, based on standardized mean differences in pain and function, the authors concluded that, overall, opioids were more effective than control interventions in terms of pain relief and function.

So let's move on to evidence from neuropathic pain states. Again, one of the early studies was done almost 15 years ago, and this was a parallel, double-blind, randomized study in patients with postherpetic neuralgia who were treated either with a placebo or a controlled-release oxycodone, with the treatment period being four weeks.

Again, both for ongoing pain as well as stimulus-evoked pain, allodynia, the group treated with opioids had a reduction in pain intensity, with a greater proportion of patients on the opioid therapy group who said their pain was improved moderately or greater, 58 percent versus 18

percent.

We conducted a slightly different design in the same population, that is, postherpetic neuralgia patients, a randomized crossover study, and here there was an active comparator, the comparison being tricyclic antidepressant. So each patient would go through three phases, either a placebo phase, a tricyclic antidepressant phase, or an opioid.

Again, we observed that during the treatment period with opioids, there was a reduction in pain intensity, and so was there a reduction during treatment with tricyclic antidepressants, and that the patients overall, 50 percent or more, preferred the opioid period and 30 percent the tricyclic antidepressant period.

So both these studies, the earlier two studies in neuropathic pain, were in patients with peripheral neuropathic pain states. And so the issue was, is it equally effective in central pain states? And a study was done by Mike Rowbotham and coworkers, where they used a group of patients that

included both peripheral as well as central neuropathic pain states, studying levorphanol. And their observation was that, overall, compared to a low-strength levorphanol group, a higher-strength group had a greater reduction in pain intensity and pain relief.

So how do we compare these drugs? One study that has been used is the use of NNT, or the number needed to treat, which, compared to placebo, how many patients do you have to treat to get one patient who has 50 percent or greater relief. And the opioids, from the randomized, controlled trials, have NNTs in the range of 2.5 to 5.5.

So how does this compare with the other drugs? So Nana Finnerup has done this for us, an analysis of all the drugs that have been used for neuropathic pain states. The size of the circle indicates the number of patients in these different studies.

So what you notice is that opioids are in the same range as the other drugs used for neuropathic pain, although the number of patients

that have been studied with the opioids have been considerably lower than the other studies.

One of the issues that has come up with the use of opioids is that the majority of these patients that are treated with opioids, such as patients with chronic osteoarthritis or patients with postherpetic neuralgia, are elderly patients. So a systematic review and meta-analysis included trials, 18 trials, trials that included patients who were 60 years or older, to determine what is the efficacy of opioids in this elderly population or older population.

The conclusion that they made from these studies is that, overall, the main change in pain intensity with opioids in this elderly group of patients, over 3,000 patients who were studied, was greater with opioids compared to placebo, the difference score being minus 0.55. And there was also a modest improvement in function in this age group.

Another controversy in this field has been, does the efficacy of opioids differ in patients

with nociceptive pain versus neuropathic pain? This has been examined in an extensive study which included 62 randomized, controlled trials.

The study included both trials that have used an enriched design as well as a non-enriched population, their idea being twofold: one, to compare the efficacy of opioids in nociceptive versus neuropathic pain states, and to determine if the enriched design alters the outcome measures.

The conclusion that the authors made, based on their analysis of these 62 randomized trials, is that when compared to placebo, the effects of opioids are similar in nociceptive and neuropathic pain states, the first two bars; and the design of the study, whether it be enriched enrollment design or a non-enriched design, did not make a difference as far as the overall outcome measure, the difference scores being in the range of .5 to .8 compared to placebo, and therefore a modest effect.

As has been described earlier by Dr. Woodcock as well as some of the speakers from yesterday, the area where data are lacking are the

long-term efficacy of opioids for the treatment of chronic non-cancer pain. The only data we have is from open label extensions of randomized trials.

Usually these are randomized, controlled trials, followed by the active drug being done, treated with an open label phase. And these have been from 6- to 12-month periods, so 18-month periods.

This Cochrane review analyzed by pooling the data from the 6- to 7 and a half month period in these four different studies, and determined that the efficacy of the opioids persisted at the 6- to 7.5-month period. And they concluded that the pain relief that appears to be clinically important is achieved long-term for patients who are able to remain on the oral opioids for the 6-month period.

They added that the strength of evidence was weak because of the fact that during that 6-month open label period in most of these studies, there was a significant dropout of patients. So based on that, although there was a difference at the 6-month period when the four studies were averaged,

the conclusion was the strength of evidence was weak. Obviously, this is an area where further studies and further evidence is required.

So when one looks at the randomized, controlled trials done over the last 15 years or so, there have been numerous trials, more than 60 randomized trials, which have compared the active drugs, such as oxycodone, morphine, transdermal fentanyl, hydromorphone, transdermal buprenorphine, and tapentadol, that have been compared to placebo or compared to each other.

So what are the kinds of conclusions you can make overall from these studies? The conclusions that I've come up to, based on these studies, is that the randomized, short duration efficacy studies using various trial designs, enriched as well as non-enriched, show that compared to placebo, opioids significantly decrease both nociceptive and neuropathic pain states; that the efficacy of opioids in nociceptive or neuropathic pain states are similar; and that there is no clear difference in efficacy of the different opioids

based on comparative trials.

I thank you for your attention.

(Applause.)

DR. DWORKIN: Our next speaker is Dr. Jane Ballantyne. She is the University of Washington Medicine Professor of Education and Research, and a professor in the Department of Anesthesiology and Pain Medicine at the University of Washington.

She has been and is currently chair of the IASP Education Working Group, and is responsible for really landmark publications, reviews of the literature in the field, looking at both the efficacy and risks of opioid analgesics. These are really critical publications, published over the last 10 years.

So we're pleased to have her here, and she'll be discussing what is the evidence for the effectiveness of opioid analgesics for chronic pain from non-randomized clinical trials, other clinical data, and also from administrative data.

**Presentation – Jane Ballantyne**

DR. BALLANTYNE: Well, thank you. I would

like to thank the FDA for inviting me here, and in particular the two Bobs, Bob Dworkin and Bob Rappaport, for including me in this panel.

I should start by saying that I have no conflicts of interest. When you see the term "MED" on my slides, that's morphine equivalent daily dose. I'm not going to keep repeating it. It's an oral equivalent, morphine calculated dose, and is used to compare usage in terms of norms and safety.

I've been given 20 minutes to cover a very large literature. So I haven't put all the references on my slides; it would just be impossible. But I have given them to the FDA, if you're interested.

Clinical and administrative data comprises observational data and epidemiological data. I want to start with this observational study because it's a seminal study that almost single-handedly changed the way we practice.

We may ask why this study of only 38 patients had such a profound influence, and I think it has much to do with the authors. They

were very high stature and highly regarded cancer pain physicians. Also, the journal in which they published, Pain, is the most highly cited of all the pain journals. These authors made a compelling case for extending opioid treatment beyond palliative care and into chronic pain management.

This is not a real patient, but she is typical of the patients we see in pain clinics. We started seeing this type of patient when we were emboldened to use opioids for chronic pain by the Portenoy and Foley article.

She's young. She has a painful and distressing disease. She's run out of options, and she's considered a suitable candidate for chronic opioid treatment. A year later, she's doing much better, and her improvement in both pain and function can be attributed to opioid therapy.

So what is the evidence in the literature that supports this clinical impression? In the year 2003, I went to the literature to find out what support there was for using specifically high-dose opioids. Through our clinical observations,

we were beginning to notice that patients receiving high doses did not have good pain relief and were not functioning well. This made them very different from the patients who were receiving low to moderate doses.

We actually didn't find any support for the high doses that people were using, but we did find support for using low to moderate doses, generally over a period of up to two years, and no longer. This 2008 evidence review on this slide found very much the same as we found in 2003. In other words, the evidence didn't really change over these five years.

Two years later, in 2010, Meredith Noble and her group published a formal systematic Cochrane review -- actually, Raj has already told you about this review -- which was utilizing prospective studies. All but one were uncontrolled studies, and they were mostly open label follow-up studies tagged onto our CTs, as you've heard.

Again, there was support for the use of and efficacy of opioids for up to one to three years,

although their conclusions were not only that you could find some improvement in pain, but that they were unwilling to make any conclusion on functional quality of life. They also said that it was not helpful, the review was not helpful in terms of assessing safety or addition risk.

But importantly, what was found, and has been notable in other reviews and meta-analyses, is that between 33 and 60 percent of patients who start chronic opioid therapy actually abandon it. And that's either because they don't find it effective or because they don't like the side effects.

So just to summarize what we learned from observational data, and there are many more studies than these two, generally these studies show improvements in pain. Although there are a few outliers, generally patients are followed for no more than two years in this type of study.

The doses are moderate. Moderate, I would say, is between 60 and 80, with a few that go as high as 200 MED, and a few really extreme outliers

go up to 2 grams MED, where there is report of good function, quality of life, and efficacy, even at these really high doses, but they are isolated reports.

Findings on function and quality of life are actually equivocal across this type of study, and these studies cannot really provide any conclusions on addiction risk.

You have already heard much about epidemiological evidence from Michael Von Korff's presentation yesterday. The epidemiological evidence contrasts starkly with the evidence from observational studies in that it does not support good analgesic efficacy or functional improvement.

There are also, as you've heard, alarming safety data. Epidemiological studies are beginning to help us understand which patients dose escalate and which tend to stay on opioids.

Judith has now been on opioids for two years, and her life in general has taken a turn for the worse. Her rheumatologists don't understand why her pain is getting worse because according to

their blood tests, her disease is no longer active. The clinicians treating her pain assume that she's developed opioid tolerance and needs a higher dose. Dose escalation for her is now happening more and more frequently.

After six years, she's not doing well at all. This is not to suggest that all patients who are started on opioids follow this trajectory. But this fictitious case does illustrate a typical progression for those patients who ultimately fail chronic opioid therapy.

I don't think many people these days would dispute that this is a treatment failure. Not only is the dose unsafe, for her no dose is enough. Neither pain relief nor function are good, and what isn't apparent on this slide but is a significant factor is that tapering for her will be distressing and may be inhumane.

Our case begins to explain why epidemiological data appear so different from observational data. Epidemiological data include all the patients who have dose-escalated and are

not doing well. They also include all the patients who are not treated in the careful practice settings that are typical of the case series and the open label follow-up studies.

Thirdly, since the 1980s when we first started doing this, opioids are being used for an increasing range of patients and diagnoses, a much wider range than was described in the original studies, including diagnoses like fibromyalgia and headache, where the clinical evidence is really quite compelling that these diagnoses don't do well with opioid therapy.

Out of several broad population-wide studies, two are worth mentioning. This study from Denmark was one of the first to alert us to the fact that on a population basis, chronic opioid therapy was not looking good. Even after controlling for disease and pain severity, which these authors did, opioid users were reporting worse pain, health, activity, employment status, health care utilization, and quality of life.

This study from the United States looked for

dose-related differences. The study was conducted across several primary care practices; 235 primary care physicians were involved.

As you can see, all the physical health domains actually deteriorated rather than improved on the higher doses, and the only improvements for the higher doses were in the emotional and mental health within mental health domains. At the lower doses, however, there were actually improvements across the spectrum.

In the U.S., there's now a substantial literature from workers' comp claims data. The primary outcome of interest in these studies is functional improvement and return to work. There are more studies than are reflected on this slide, but these are four key studies.

In all these studies, there is a demonstrated delayed return to work associated with opioid treatment, particularly when it's used early during the post-injury phase. In the Webster paper, increased disability and cost is correlated with increased opioid dose. In the Volinn study,

odds of chronic work loss are 11 to 14 times higher for early opioid-treated patients.

Since no assessment of effectiveness can be complete without consideration of safety, this is just a reminder that there's now compelling evidence that the high doses of opioids used by pain patients contributed to deaths seen in these patients.

If we accept that low to moderate doses of opioids are potentially useful, but that high doses of opioids are often ineffective and are unsafe, then an important research question is which patients escalate and why? The literature is actually very weak on this. There are four studies that I'd just like to review briefly because I think it's an important area for research, and this just emphasizes how little we know about it.

There's a study published by Portenoy, et al. in 2007 that was actually included in the overviews that I showed you. It's a registry study looking at OxyContin, prolonged OxyContin use over a period of three years. This is actually one of

the furthest out of any of the registry-type studies. Only 39 patients actually reached three years, but that's an artifact related to the fact that the study was closed early.

Forty-four percent needed dose increases by month 3, which we expect, because we usually titrate up until we find a therapeutic dose. But even after 12 months, 8 to 13 percent of patients still needed a dose escalation at each time point that was measured.

Schneider and Kirsh in 2010 did this retrospective chart review so that we're looking at the single clinic charts over 56 months. Of those patients, 40 percent did reach a stable dose, but that stable dose was quite high -- the mean was 180 MED -- and 38 percent of those patients never did stabilize, so they continued to dose escalate or they developed aberrancy and the treatment had to be discontinued.

Naliboff in 2011 published a really interesting RCT in which a group of patients that were allowed to escalate per protocol was compared

with a no-escalate group. Both were allowed breakthrough medications, so both did escalate to some degree, but the escalating group, by 80 percent and the non-escalating group by 16 percent.

What's interesting about their finding is that looking across the whole study and the end result, there were no differences in pain or function between the two groups, even though the escalating group had reached much higher doses. The benefit for the escalating group was, however, that each time they dose-escalated, they did get some benefit, but it was short term.

The Martin study is an epidemiological study that looks at claims data for up to 2.3 years, and follow-up for just over 4 years. Two-thirds of the patients that received more than 90 days of treatment actually remained on treatment years later, and remaining on treatment for years was strongly associated with reaching high doses, doses greater than 120 milligrams per days; also with misuse and with intimate and prior exposure.

This slide attempts to illustrate why

tolerance and dependence are important in the clinical picture of dose escalation in failed chronic opioid therapy. Tolerance and dependence are inevitable adaptations to continuous opioid use. We can argue about the details, but no one would argue with this broad general statement.

The figure in the top right-hand panel is borrowed from "The Addiction Experience." Recreational drug users initially take drug to get euphoria, but ultimately need drug to avoid dysphoria.

Although the mechanisms are different, we see something very similar in the case of failed opioid pain treatment. Pain relief is good to begin with. But ultimately, failing patients are taking opioids to avoid worse pain, but are not getting good pain relief.

In the bottom left-hand panel, I've tried to illustrate the close relationship between tolerance, dependence, pain, and mood. Tolerance is affected not just by drug factors but also by psychological factors. If an increase in tolerance

isn't satisfied by an increase in dose, then withdrawal symptoms arise. Pain and mood may deteriorate, and withdrawal symptoms will drive craving and opioid-seeking.

In the interests of time, I'm not going into this literature. Suffice it to say that there is now a sizeable literature suggesting that after a complete taper off opioids, pain and function are seen to improve.

There may be a significant relapse rate, but what is interesting is that immediately after a complete taper, pain does not get worse; rather, it gets better. This is very different from what we see during a taper.

Finally, I just wanted to point out that there's now extensive literature on what my colleague and friend Mark Sullivan calls adverse selection. Patients who stay on opioids tend to have complex psychosocial comorbidities, especially substance use disorders and, importantly, post-traumatic stress disorder.

This is not just about risk of misuse or

addition. This is about risk of becoming like Judith, who will find it very hard to get off opioids but who's not getting good pain relief or functioning well, and who may be at risk of death, especially if her dose escalates any further. Screening for substance abuse risk is not enough.

To summarize, observational data support good analgesic efficacy for low to moderate opioid doses over one to two years. They also suggest, importantly, that many patients choose to discontinue chronic opioid therapy. Epidemiological data present a less positive picture, with analgesic efficacy, functional restoration, and safety not being supported.

One way to look at this is to look at the outcomes from a cohort of patients compared to a population at a single time point or a single time range. Although we don't have any handle on how many patients do well and how many do badly, we do know that approximately 50 percent take themselves off opioids.

This means that regardless of how many do

well versus badly, both groups will be exaggerated when turning from the cohort's lifetime outcomes to the population at a single time point.

Adverse selection would also suggest that over years, the proportion of patients that do badly will increase. I don't think that's going to happen because I don't believe we're going to continue on the trajectory we've been on recently, but I do think it partly explains what we're seeing now.

In conclusion, the problems seem to be centered on high-dose uses. The safety data are compelling, and even though causation can't be proved, this evidence has to be factored into any assessment of effectiveness.

Lack of convincing data on efficacy for high-dose opiates is an additional reason to state that on the basis of current evidence, effectiveness -- that is, benefit versus risk -- of high-dose opiates is not proven.

I would just like to conclude by saying that what I believe the important research gaps are. We

don't know what characterizes the propensity to dose escalate, whether in terms of patient characteristic or drug characteristics. We also don't know -- we have no idea -- how many who stay on, don't escalate, and do well; in other words, what is the size or what characterizes this cohort that we believe are the patients that do just fine on opioids? We need to target this group because this group will justify the continued use of chronic opioid therapy.

Finally, can we identify a cutoff dose in terms of safety that should become a safety standard?

Thank you for your attention.

(Applause.)

DR. DWORKIN: Our next speaker is Dr. Dennis Turk. He is the John and Emma Bonica Professor of Anesthesiology and Pain Research in the Department of Anesthesiology and Pain Medicine at the University of Washington.

Dr. Turk has been president of the American Pain Society, and for about the last 10 or 12

years, editor-in-chief of the Clinical Journal of Pain. It's a pleasure to have him with us. And he is going to be discussing the limitations of existing data on the efficacy and the effectiveness of opioid analgesics for chronic non-cancer pain.

**Presentation – Dennis Turk**

DR. TURK: Thank you, Bob. And I want to commend the FDA for convening this very important meeting, and especially thank the audience for participating, taking the time to be here to discuss what I believe is a critical issue that you've heard from our speakers.

I've been given the dubious distinction of trying to look over the presentations that you've heard before to try to identify some of the limitations. And obviously, in the time I have available, I'll have to do some rapid speaking, which means you'll have to do some aerobic listening.

My disclosures, so that you can see them. And they are on the website.

Evidence is what is evident based on my

experience. The plural of anecdote, however, is not evidence. But there's as much disagreement as to what qualifies as evidence as there is to what constitutes good clinical practice.

So what I'll be trying to do is look at the evidence that you've been seeing before you, but also talk about what are the limitations of that information and how does it influence how we can interpret the information that we have available. And how does it help us start identifying what are the critical questions that we need to address as we move forward to get answers to the types of questions that we're all here and concerned about.

From my perspective, we've been asking the wrong question in many of these studies. Are opioids or any medications safe and effective in the treatment of patients with chronic pain?

That seems to be the question that's been addressed in the majority of those studies, but that tends to create a false dichotomy. Is it yes or no? Are opiates good or not good? Is it a zero response or a 100 percent response? How do we

decide?

So we really need to start thinking about what I consider the right questions, and many of which have already become apparent to you as the two days have gone on.

Are opiates more clinically effective than alternative treatments? Do the benefits outweigh the adverse effects? On what criteria? Delivered how? With what adverse events or effects? For whom and for how long? And are opiates more cost-effective than alternative treatments? Now, we're not focusing on the latter question in this particular presentation, but the previous ones are ones that we should be considering.

So what's the criteria of success for opioids? Well, what's important to the patient? What's important to the health care provider? What's important to the payers? What's important to employers? And what's important to society? Are the same outcomes equally important for all of those groups?

Well, if we ask the patient, and we heard

many of them discussing this yesterday, elimination of pain is what they would prefer, or at least a significant benefit or reduction in their pain. The evidence, as you've seen, is modest and in fact meets that goal. Adverse effects are common, as we've seen from Dr. Ballantyne's presentation and Dr. Von Korff's presentation.

There's patient satisfaction. How much relief would be needed to be reduced for the patient to be satisfied? And that's going to depend to some extent on the severity of the pain level that they begin with.

What about functional improvements? Well, payers are particularly concerned about functional improvements and also about health care utilization. Employers may or may not care much about pain reduction and patient satisfaction, but they want to know if they return to work or go off of disability. And society is concerned about diversion. Each of those outcomes are important, but the emphasis to the different groups varies. Who decides? Each group makes their decisions.

Now, I'm going to talk about some limitations of randomized, controlled trials in general, and I'm going to talk about, therefore, the limitations of meta-analysis and reviews in general. And then I'll say that all those concerns apply to opioid trials as well as non-opioid trials.

So some of the limitations, and I'm only going to be able to cover some of them. They include clinical trials may not represent what happens in clinical practice. These are volunteers, or they're people who are referred.

I can tell you, in some trials that I've been involved with, we started looking at the referrals that we've been receiving for these trials and found out they're quite different from the average persons that we're reading about in the literature.

When we asked the physicians who were referring to our particular clinical trials how come we were seeing such distressed and troubled patients, they said, oh, well, we knew you had

psychologists available, and therefore we were sending you our more difficult patients. So they may not be representative of the people out there who may have these particular problems.

There's difficulty in the blinding of the patients. Often we hear about using placebos, which common times are inactive placebos, and the patients or the subjects that are participants in these studies may be well aware of that.

When we look at the active placebos when they're used, we'll see big differences in the placebo response rate to active versus inactive placebos, but inactive placebos are rarely used.

What about the patient's willingness to be randomized to a clinical trial that's going to include placebos? Are these patients representative? Will all of the patients that are out there who are taking these types of drugs be willing to be randomized to a trial in which they may be receiving a placebo?

There's also a technical bias that's in favor of the research we know how to do or that's

easy to do. Monotherapies, we have good experience. We know how to do those. But combination therapies are much more difficult, much more expensive to perform.

There are a number of questions to consider in systematic reviews. And although there have been a number of systematic reviews, and you're going to hear more about these later, in the period of 2008 to 2010, a series of different systematic reviews led to guidelines based on meta-analyses. And interestingly, these guidelines lead to very different conclusions. And yet the guidelines are based on the evidence coming out in the same rough time period, 2008 to 2010.

So how is that possible that we would see very different results with meta-analysis, very different conclusions, very different clinical practice guidelines that are supposedly looking at the same literature.

We can look, for example, at the American Pain Society, American Academy of Pain Medicine treatment guidelines. They made 25

recommendations. They did not rate any of the recommendations as supported by high-quality evidence, only four of the recommendations reviewed as being supported by even moderate evidence. So these clinical guidelines are being promulgated, but they're based, acknowledged, on very limited information.

So some questions for us to be considering when we look at systematic reviews in meta-analysis, who sponsored the development of these particular meta-analyses or reviews? And I'll give you an illustration of why that becomes particularly important in a moment.

What are the inclusion/exclusion criteria that are used in the studies that then go into those meta-analyses? Are, in fact, the types of patients who are included in these trials representative?

I was once involved in a trial, or was invited to be involved in a trial, on fibromyalgia patients, and one of the exclusion criteria was that patients could not be depressed. Well, if

you've ever dealt with fibromyalgia patients, as I spend a lot of time doing, you realize that that's very small. In fact, 80 percent of our people with fibromyalgia in our clinical trials have significant levels of depression. So if we can only look at the 20 percent, how representative are those and what are we learning about fibromyalgia patients in response to those treatments?

What was the duration of the studies? You've already heard that the randomized, controlled trials have been very short duration. Even the open label extensions often are quite short. And yet we're asking to put patients on these treatments for long periods of time.

Who conducted the computerized searches that actually selected the articles that went into this particular meta-analysis that we may be looking at? Did the authors of the meta-analysis rely only published studies, which may over-represent positive trials? As we know, the likelihood of a study getting published is higher if, in fact, the results are positive than if they're negative.

Who actually performed the data analyses in these particular studies? Who prepared the manuscript? And again, I'm going to illustrate why that's important for you shortly. How timely are the reviews? That is, if the meta-analysis is published in 2008 or 2010, how far back did they go? How timely is that? The publication process can take anywhere, from beginning of writing a manuscript till it appears and sees the light of day of day, or two years. So they're already out of date by the time that we see them.

Results provide information about a highly selective group of individuals. What is the relevance of the group data for any individual patient? For example, if you have a depressed low back pain patient with a history of substance abuse, work loss, and pending litigation, how likely will you be able to extrapolate from the typical randomized, controlled trial that uses those as exclusion criteria?

In fact, those are standard exclusion criteria in the majority of the studies that we

see. But when Dr. Ballantyne mentions Judith, the patient she sees, she would probably not have made it in some of these particular trials. Definitely wouldn't have been the typical patient that we see or our fibromyalgia patients wouldn't be because they often are depressed. They often have histories of substance abuse. They often have work loss and pending litigation.

Who graded the quality of the studies? Was there any demonstration of inter-rater reliability of the coding of these studies? And having been involved with these studies, I can tell you the agreement among raters is often not particularly high, and yet if we don't actually make an attempt to determine if inter-rater reliability has been performed, we really don't know.

What system was used to rate the evidence that goes into these trials? There's over 49 different systems available. So your choice of what's inclusion or exclusion criteria varies depending upon which of these systems you're using.

I should have mentioned at the beginning,

I've tried to put citations down for all the points that I'm making at the bottom of these slides. I know I'm going through them very quickly. I have made the full references available to the FDA, who may or may not make these available on their website. I'm not sure what they will be able to do with those. But they are available if you want to see them.

So let's look at, outside the opioid area but still within the pain area, why I think it's important for us to be concerned about the kinds of questions I just raised. This is an illustration of a problem, for example, spinal cord stimulators, or SCS, for low back pain. Now, I want to give you an example of two different reviews or meta-analyses of the literature that led to somewhat different conclusions.

One of the studies was performed by Taylor, et al. And they looked at the literature -- and this was as of 2004 -- and they found there was one acceptable randomized, controlled trial and 72 case series of spinal cord stimulators. They judged the

case series to be of poor quality. The best predictor of success in the case series was poor quality of studies and short duration and inclusion of failed back surgery syndrome. The poorer the quality of the study, the shorter the duration of the study, the more likely there was a positive effect.

In the randomized, controlled trial, they determined that 37.5 percent of the patients showed at least a 50 percent or greater pain reduction. So compare that to another study, another meta-analysis, done by Cameron. This found, using his criteria, 16 studies could be included in this particular trial, two prospective controlled trials. And they conclude, or he concluded, that 62 percent of the patients reported a 50 percent pain reduction.

Now, notice the difference. Notice the year that these were done, both conducted in 2004. What could explain the differences? Well, one possibility is that Cameron was an employee of the company that manufactures spinal cord stimulators.

Now, that doesn't mean that this is a bias, but it's possible that it did contribute to this.

So we've got to be concerned about who did the analysis, who's funding the analysis, who's putting this stuff together. And are we seeing something I can call evidence biased publication?

The positive results, as everybody mentioned, are more likely to be published, and that's sometimes referred to as a file drawer problem. For every study that gets published, there are a certain number that had negative results, that never see the light of day. And there's a way of calculating or estimating what those effects might be.

Industry-sponsored trials are more likely to report positive results than non-industry-sponsored trials. And this has been the publication to support that. Yet 80 percent of all clinical trials are funded by industry.

So what would have happened if, in fact, we had an equivalent number of studies that weren't funded by industry? What would the results look

like? The evidence biased practice of selective reporting of results, with data mining by study sponsors.

I should say the study sponsors may be investigators from non-industry-sponsored studies because I've seen data mining, and all of you that do research have seen this same thing occurring. But these are concerns that we have because when we're making decisions based on published literature, we have to understand what goes into some literature being published.

Some paradoxes for us to be thinking about. Meta-analysis that was initially created as tools intending to ease clinical decision making is becoming progressively more complex. The growing complexity is rendering evidence-based practice less and less able to offer simple, clear, useful solutions to real-world problems; 49 different ways to judge the quality of the studies, and different criteria being used, and which studies you will include in your analysis.

How is the practitioner supposed to make

sense out of what was originally designed to help them? That is, the meta-analysis should help guide evidence-based practice, and yet we're getting more and more complicated.

There are often more systematic reviews and meta-analysis than the RCTs published on the topics. Think about that for a minute. There are more reviews and more meta-analysis than the number of studies.

So, for example, in one of the slides that Dr. Ballantyne showed, there were four studies that were included in the systematic review. There have been more than four systematic reviews of those four studies.

Reviews often conclude -- and I love this; I think I have it programmed in my computer as a macro -- the quality of the studies are not good enough, effect sizes are too small, more and better research needed, and long-term prospective studies are required before valid conclusions can be established. That helps the FDA tremendously when they have to look at the information and say, how

are we going to make decisions?

I don't want to belittle this because from the perspective of the FDA as I see it, they are concerned about doing the best to provide safe and efficacious treatment, and they have to base it on the available evidence. So therefore, they are in the dilemma of having to deal with all of the issues that I've been raising as we go along.

Now, some more paradoxes. These are two studies, one by Raj, who looked at a Neurology article. He looked at painful diabetic neuropathy. I believe he showed it to you already. And then another one on chronic back pain.

What I want to draw your attention to is notice that the inclusion criteria for a typical clinical trial is a rating of 4 on a zero to 10 scale, which has been the cutoff between mild to moderate pain.

This is just looking at the trials, and the first on the left is looking at placebo versus opioid versus TCAs. But most importantly, interesting, look at the level of pain reduction,

or the level of pain severity, at the end of the trial. On average, it was substantially higher than 4. If we look at the chronic low back pain trial, it's the exact same thing. And here their entry criteria was a rating of 5, so it's even higher pain.

Now, what this illustrates is that all of the patients, the majority of the patients treated in these trials, their level of pain at the end of the trial would be sufficiently high for them to enter the next clinical trial because the clinical trial didn't produce pain at a level below the entry criteria.

So despite the fact that these are both showing beneficial effects, they actually don't really lead to reductions of pain to a level that the patient might say is satisfactory because they still have a moderate level of pain.

So some more paradoxes. A substantial number of patients in these studies would meet the criteria after successful treatment and be eligible for the next trial.

Patients excluded in clinical trials are just the ones most commonly seen in clinical practice, and I've mentioned that already. Trials tend to exclude women of childbearing age, presence of comorbid medical and psychiatric conditions, histories of substance abuse, multiple pain locations, treated with multiple drugs, compensation/litigation issues. That's who is being treated in the pain clinics. That's who's being treated by the primary care providers.

So how do you generalize the results from those trials that have these limitations and restrictions, and inclusion and exclusion, to what's going to be used with a population of people, some of whom we heard from yesterday in the open forum?

Some limitations of the opioid trials that we've already seen. Well, there's an additional limitation on generalizability. There's a referral and recruitment bias; volunteer bias; excluding those taking other medications; that has an effect.

Duration. If we look at the average

duration of these trials -- you've heard this mentioned already -- the average duration is about 5 weeks, with a range from 1 to 16 weeks for the randomized, controlled trials. So we're asking to put people on long-term opioids, based on what we can learn from randomized, controlled trials of approximately 5 weeks.

Maximum dosages. Is it fixable or flex dosages? We keep hearing about 120 milligrams, 180 milligrams. The literature really has very little information about over 180 milligrams, but much higher numbers are used in practice. In the State of Washington, the workers' compensation system showed there were a percentage of patients who had over 3600 milligrams of morphine equivalent. We know nothing about what happens with those.

How do we blind people in these particular trials? How do we blind them to the opioid and the placebo? Can we blind them?

What's the difference between statistical significance and clinical significance? So many of

these trials show a statistical significance, but are those, in fact, clinically important?

I'm going to be running out of time in a moment, so I'll speed up.

Then what are the comparators? Are they active comparators? Inactive comparators? Do we have placebo studies? What about these high -- we've already seen the high side effects. And the dropout rates and the loss to follow-up, I'll just show you -- we've heard enough about those -- in a moment, and also the Noble study, what they reported. There's low assay sensitivity/high placebo response rate. Outcomes rely on patient self-report. They often don't pay attention to all those other kinds of factors that I said were particularly important as far as return to work or off of disability.

Open label trials. Uncontrolled extensions. Registry trials. This is the study that we heard from Portenoy. They started out with 831 patients in this registry trial; they ended up with 233 that they entered into the open label phase. 127 of

them discontinued prematurely. One hundred patients were actually left. So we started with 831 patients, and we're left with about 12 percent of those patients who were in this particular extension.

So what can we know about those patients, and how representative? During the open label extension, greater than 3 months, pain increased 9 percent and 90 percent; 18 percent and 65 percent; and 44 percent had an increase of more than 30 percent in their medication requirement over the time period. There's a selection process.

I'm going to have to get out of this. This is the Noble study that you saw. But she reported -- she and her group reported that looking at randomized, controlled, open label phases, 44 percent of the patients dropped out of the open label extensions for reasons of either efficacy or tolerability.

So think about what happens. To get into the open label extension, they had to have done well enough in the randomized, controlled phase.

So we've dropped out the people who were having intolerable side effects. We've dropped out people who have not effective levels of treatment. So they go onto the open label extension, and in the open label extension, 44 percent are dropping out.

A final problem, a difference is not a difference unless it makes a difference: overall reliance on statistical significance, inadequate attention to clinical significance and meaningful results, or minimally important difference or substantial benefit. Although there may be statistically significant differences between treatments, the effect sizes may be small, as we've seen. And citing the title of one article, "It's Good to Feel Better, But It's Better to Feel Good."

So let me just, because I'm running out of time, let you just look at these. These are some unresolved questions that need to be addressed that we've talked about very rapidly. And I'm sorry I've just gone over and I can't go through these with you.

But there are a number of different issues

that need to be addressed that, when we talk about the agenda for research, these may be things thought we'll, in fact, want to be talking about as we go through the discussion, unsolved questions. These are characteristics of studies that we just need to find out more about.

I know that you didn't read those, and that's okay because they are going to be available to you on the website. You can look at these, and we'll have these in the discussion. But the point is, you've already heard numbers of unanswered questions, unresolved concerns, about the design, the drug, the disease, the trial structure, the enrichment procedures, opioids on entry, dosing titration, concomitant medications, rescue, duration, endpoints. All of these are going to be things that we need to be paying attention to as we go forward in our research, and we can start saying, what's the priority of these.

We really need to go to a significant perspective about these things. There's a disconnect between the evidence that we have and

what people seem to be saying on both sides of particular issues.

We have tradeoffs that we have to pay attention to, and that's the internal validity of the study and the external validity of these studies. The more we control things, the less it is something that we can generalize from. And we also have to come to a balance between the costs and benefits.

I apologize for the speed with what I ran through that last set of slides with what those issues are. But I think we are going to have an opportunity to discuss these when we get to the discussion section. So thank you very much.

(Applause.)

DR. DWORKIN: Our next speaker is Dr. Michael Rowbotham. Dr. Rowbotham for many years was professor of neurology in the Department of Neurology at University of California San Francisco Medical Center. He's currently scientific director at the California Pacific Medical Center Research Institute.

He's been a member of the IASP council. He's treasurer-elect, I believe, of the IASP. And I think, most importantly, he did, starting in the 1980s and then continuing through the 1990s, really landmark research on what we now call patient phenotyping, personalized pain medicine, focusing on the mechanisms of postherpetic neuralgia and trying to figure out whether the mechanisms, as revealed by patterns of signs and symptoms, can provide a guide to mechanism-based treatments. And so those were really fundamental studies.

Dr. Rowbotham will be putting the previous talks in the context of what alternatives are there to the use of opioid analgesics in the treatment of chronic pain in light of existing evidence and limitations.

**Presentation – Michael Rowbotham**

DR. ROWBOTHAM: Thanks, Bob. It's a pleasure to be here and to address this audience.

So my talk is about alternatives to the use of opioid analgesics in light of what we've heard. Some of what I'm going to say today is going to

remind you of things that the previous speakers have said, and I'll be adding in a bit of my own perspective on some of these topics as well.

First of all, to go through my disclosure list. None of these engagements include anything related to opioid analgesics, and for the most part, they're looking at phase 1/phase 2 studies of new non-opioid analgesics for chronic pain.

So when I talk about alternatives to the use of opioid analgesics, I'm going to focus primarily on drugs because opioids are a class of drugs. And so we should focus on other drugs that might act as a substitute or an alternative to opioids.

There are a number of other options, and on this first group, looking at ones that are not really alternatives to opioids but things that should really be considered and implemented in all patients with chronic pain.

So, for example, dietary factors have not really been very well studied, but are potentially really quite important. And I'll point you to a paper that will be coming out in the Journal of

Pain in the next few months. It's in press, a topical review by Ray Bell and colleagues on dietary factors, especially some things that can be increased by changes in diet or that are available as over-the-counter supplements, things like alpha lipoic acid and acetyl L-carnitine.

I also want to point out the CAM approaches in a very nice paper by Lee and Raja in pain about a year ago on this, although not all complementary and alternative medication approaches are completely risk-free. And I'll point you to a review on the hazards that have been reported with various kinds of acupuncture and some other therapies that would be considered in the CAM sphere.

Cognitive behavioral therapy, mindfulness-based treatments, education group programs, can have tremendous benefit and are essentially risk-free. Exercise regimens can be extremely useful, and for disorders like fibromyalgia, conditioning and gentle exercise programs are certainly as effective as any other type of approach.

Now, what about going to the other end, going beyond the oral medications? So there's certainly the device-based treatments, and there was some discussion just in the last talk by Dennis Turk on that.

What I mean here are spinal stimulators, other kinds of stimulator approaches, and implanted drug pumps. These, of course, are extremely costly initially and for maintenance, and their long-term efficacy relative to drugs, both opioid and non-opioid, is really known or at least uncertain.

There's also a range of nerve blocks that can be used, and in general, there's little prospectively gathered data on their long-term benefit. Most pain clinics, the staple is use of epidural injections and epidural steroids. And they're often used even for types of pain where there is no clearly demonstrated benefit. These are also, of course, quite costly and have a number of hazards associated with them.

Then I'm including here the high-strength capsaicin application, Qutenza, which was approved

in the past couple of years. And although this showed efficacy from two weeks onward, there was substantial initial pain worsening in many of the patients.

This is something that's really another type of a procedure. It's administered in the office, and it's not something that you can just write a prescription for and the patient can take it with them.

Now, turning to the question of medications, the things to think about are, what is the safety and tolerability, especially in older persons who may already have a problem with polypharmacy they're on, medications for high cholesterol, for high blood pressure, on and on.

The other is, patients want to have some evidence fairly quickly that their pain is being addressed and relieved. And then, of course, the ease of use as well as the ease of monitoring is really quite important, both to the patients and to their prescribers.

So something that is a fairly simple dosing

schedule, and also where the dosing is fairly consistent; in other words, it's fairly predictable what will be the efficacious dose, and also fairly predictable what dose level would produce an unacceptably high risk of adverse effects.

So what I'm going to touch on here are four categories of medications that are the most widely used for chronic pain: the antidepressants, and anticonvulsants, and the topicals, and of course, all the other talks have been on opioids.

First of all are the antidepressants. These have been around the longest in their use for chronic pain, with some of the earliest landmark studies being of the tricyclic antidepressants. And in general, these have been highly effective in most pain disorders.

They not only have a serotonin and norepinephrine reuptake blocking effect, but the tricyclics all have in common their effects as relatively nonselective sodium channel blockers. In fact, you can use drugs like injectable amitriptyline to produce a nerve block. It's that

potent as a sodium channel blocker.

The tricyclic studies, though, have very important limitations. One, they're almost all very old studies now. They generally were small crossover designs. Patients were allowed to enter those studies even if they'd already been on tricyclics for a considerable period of time. And these were generally conducted in an era before many of the newer medications came along. As I'll get to in the next slide, these drugs also have considerable hazards associated with their use.

For the serotonin selective reuptake inhibitors, there was great interest in those when they first came out as potential alternatives for treating pain. But unfortunately, they almost all had either no efficacy or greatly reduced efficacy compared to a tricyclic.

More recently, the serotonin/norepinephrine selective reuptake inhibitors like duloxetine, milnacipran, and venlafaxine have had evidence in various randomized, controlled trials of being efficacious, with duloxetine clearly being the most

intensively studied, and now has a labeling indication for more than one type of chronic pain.

In this drug, when one looks across the different trials, almost all of which were sponsored by the manufacturer, the effect size relative to placebo is fairly consistent.

So going back to tricyclic antidepressants, this is a list from an old publication of just commonly reported adverse events. And these are almost all enough, each individual one, for patients to be happy to discontinue a tricyclic antidepressant and go on to try some alternative medication.

In addition, all the tricyclic antidepressants and venlafaxine have a high fatality rate in an overdose situation compared to serotonin selective reuptake inhibitors. So unlike an opioid overdose for which, if you get to the patient in time, there's drugs like naloxone to reverse the effect, there is no antidote to a tricyclic antidepressant overdose. And these are really devastating types of overdoses to try and

treat in an emergency room situation.

Now, one may ask, how good are tricyclics compared to opioids? And Dr. Raja showed you data from his paper, which is really a landmark study, a three-period crossover study, looking at a tricyclic antidepressant, and opioid, and an active placebo.

What he showed was that, overall, the opioid was rated the best and produced the most pain relief of the three compounds. But that's one of the very few head-to-head trials where, in the same study, patients received both an antidepressant and an opioid and could compare the two. I'll go into one other one that also crossed drug classes in a moment.

So the problem, though, then, is where do the tricyclic antidepressants fit into the overall treatment regimen? And for this, it's very hard to tell because in general, patients who would go into a trial of an antidepressant are really quite different than ones who would go into a trial of an opioid.

If you talk to a patient who's eligible, maybe, for many different clinical trials, they usually have very strong opinions about whether or not they would be willing to go into a trial of an opioid. And so there's a lot of self-selection against going into trials of opioids. Patients say, I just wouldn't even consider going into a study of a drug like morphine or methadone, or they've heard about oxycodone, and they just wouldn't even consider going into a trial like that.

So let me turn now, then, to the anticonvulsants. This is a large and diverse family of medications which generally have, overall, received quite intensive study, although there's so many different choices that only a few have been adequately studied.

So carbamazepine has been around for many years. It's got an indication for use for trigeminal neuralgia, but generally hasn't been studied with more modern methods.

Lamotrigine had some interest, and some of

the trials were positive; others were negative. It was unclear, really, how efficacious this medication was for pain. Same story for oxcarbazepine.

Topiramate was the subject of four fairly large trials for diabetic neuropathy; three, the drug was a failure compared to placebo, and the other one showed modest benefit.

Lacosamide is the newest of the group. It's a partially selective sodium channel blocker. It was found to be effective enough in the trials to get a labeling indication in the E.U., but not effective enough to be recommended for approval for neuropathic pain in the U.S., and didn't receive that label.

There's some anti-arrhythmic medications that also have some mixed evidence for efficacy, such as mexiletine, but it has a fairly severe adverse event profile.

None of the sodium channel blockers have been compared head-to-head in a crossover type of format or a randomized format with an opioid.

Now, turning to other mechanisms, the two most intensively studied ones are pregabalin and gabapentin. Levetiracetam has also received study through one fairly large trial for postherpetic neuralgia, in which it failed to show an effect. So I'll concentrate, then, on gabapentin and pregabalin.

So these two drugs are both FDA-approved for pain. The mechanism of action is thought to be on a subunit on neuronal calcium channels. They both require an active transport system to get across the intestinal wall. They're generally well-tolerated.

Dizziness, sedation, and to some extent peripheral edema are very common side effects; it's enough to cause a significant number of patients to stop using them. And they need to have the dose adjusted for renal impairment. But they don't have major drug interaction problems. Generic gabapentin is available now, and there's some other still patent-protected versions of gabapentin that are available. And in the next few years,

pregabalin will also go off patent.

So one thing that's interesting about these drugs is that they have a fairly rapid onset of action. This is a study that was published in 2005 of gabapentin for patients with subacute herpes zoster pain, showing that if you give a large single dose of gabapentin, 900 milligrams, you could see an effect within a few hours after medication administration on both the pain and the allodynia that could be demonstrated on examination.

In some of the large clinical trials -- this is Andrew Rice's study, now more than 10 years old -- they were able to show that there was a significant reduction in pain for postherpetic neuralgia by the end of the first week.

So these two drugs generally start to show at least some benefit quite quickly, and using these medications preoperatively is fairly common to try and prevent postoperative pain and reduce postoperative opioid requirements.

Now, is there good data on gabapentin or

pregabalin compared to opioids? Well, a couple things can be said about that. One is there was a trial, actually, where patients with diabetic neuropathy were randomly assigned to get either a tricyclic antidepressant, pregabalin, or placebo. And in that particular study, the tricyclic antidepressant was effective, but the gabapentinoid drug was not effective. So they seem to be less effective than the tricyclic antidepressants.

There has been one study, a four-period crossover study by Ian Gilron, where he looked at morphine alone, gabapentin alone, and then the combination, with a placebo control. And although the statistics weren't really trying to computer each particular arm so much against each other, a greater effect was seen for the opioid as compared to the gabapentin, but that the combination worked better than either drug given alone.

Now, turning to the topicals, I just want to point out that these are generally intended to have a local effect, not a systemic effect. There are transdermal drugs available, including transdermal

fentanyl, but the idea with the topicals is generally to produce an effect directly where the drug is applied. And the reason for that is that you get the action concentrated where the pain problem is, and you greatly reduce the risk of systemic adverse effects.

So the lidocaine patch has been around for a long time now. It has a protective vehicle for patients with touch-evoked allodynia from PHN, and it's widely used both on label and off label.

There's a number of nonsteroidal anti-inflammatory drug topicals generally approved for some type of osteoarthritis. There's capsaicin available both over the counter and on prescription in the high-dose strength.

Many patients who are seen in pain clinics are getting a vary of different medications created by a compounded pharmacy in some kind of topical vehicle. So I see patients that have a topical cream that may have a little bit of an opioid. More likely it'll have something like ketamine and gabapentin and maybe some local anesthetic, all

mixed together. And those really only have anecdotal evidence for efficacy; generally, they've not been subjected to any kind of prospective trial.

Except for the NSAIDs for the arthritides, the benefit of these various topical approaches for disorders other than neuropathic pain is somewhat uncertain.

So, now, in practice, most patients come in, and unless they really do well on a monotherapy, they're put on some type of polypharmacy regimen. And so the goal is to combine approaches that have some evidence for efficacy. But as Dr. Turk pointed out, there's only a limited number of prospective studies looking at combination therapies.

Of course, you want to avoid some kind of unfavorable drug interaction or just avoid duplication in order to fill out a regimen. And it always makes sense to eliminate ineffective treatments before going on to a new treatment; it makes it much easier to monitor the patients. And

for therapies that only have anecdotal evidence, those should really always be second- or third-line approaches.

In my last few slides, I just want to go through a couple of additional caveats. One is one that Dennis Turk brought up, and that is, how representative are the subjects in efficacy trials? Then second, how consistent are the results of trials? And third, what proportion of the available data is accessible?

One thing I want to point out before going on to this is that what was presented very nicely by Jane Ballantyne is all the data from these longer-term, often observational or epidemiologic approaches, where they're looking for how sustained the benefit is of opioids. And generally, for non-opioids, this data is just completely absent.

So people are going after compounds like gabapentin, pregabalin, amitriptyline, to try and ask these same questions: How many patients are staying on them for years at a time? How much is it helping patients go back to work? What are the

kinds of long-term benefits and sustained pain relief seen with these non-opioid approaches? There's really very little data on that.

So first of all, about who are the patients in the clinical trials, this is a paper from the New England Journal in 2000 looking at patients with newly-diagnosed epilepsy. And this database has been updated and was just published in the last year, but the results are essentially the same.

So first they took a group of patients, newly diagnosed, 470, and they tried the first anti-epileptic drug. And with that, the patient became seizure-free -- no seizures at all -- in 47 percent. So they split the group into about half. And it turned out it made no difference whether you used a new anticonvulsant or one of the old ones; just half the group became controlled with that first drug.

With the second anti-epileptic tried as monotherapy, you got another 13 percent to seizure-free status. But you still had 40 percent who had uncontrolled seizures. So they went on to a third

therapy, and now your yield was starting to get very small. You got 1 percent more to seizure-free status, and you still had patients with uncontrolled seizures, nearly 39 percent of the entire group.

When you went to duo-therapy, fourth trial, fifth trial, sixth trial, it still was pretty much the same result. You salvaged a very small proportion of these patients with these additional drug trials.

Now, many years ago when there were very few effective therapies other than opioids available for patients with chronic pain, especially neuropathic pain, when a patient was enrolled in a clinical trial, they were often relatively naive to treatment. But now almost every patient, certainly every patient that comes into an academic pain center, has been tried on the gabapentin-type drugs. They've been tried on one or more antidepressants. And they've usually been tried on several opioids by the time they come there. In other words, they really have had quite a bit of

treatment exposure over time.

These patients are like this group here, where the likelihood of any additional treatments, even experimental treatments, making them pain-free or having a very large impact on their pain is probably really quite low. So the trials are skewed toward lack of effect.

Now, does that mean that the effects in clinical practice, especially in a primary care setting, are much better? The answer is, perhaps not. There's not as much good prospective, randomized data on that. But for drugs like amitriptyline, in a paper by Toth, et al. published about a year and a half ago, he found that the number needed to harm and the number needed to treat with the tricyclic antidepressants was exactly the same. It was about 6 to 7.

So if you treated a patient in his practice with a tricyclic, you were just as likely to improve their pain as you were to cause them significant harm.

The second thing that is important is that

when drugs are developed and then submitted for efficacy approval, there may be many, many trials, only a few of which are the pivotal efficacy trials.

Then lastly -- and this is my last slide -- is that there's much data that's just difficult to access, if not impossible to access. And this is a pilot study that was funded by ACTION called the RReACT Database, where we looked at clinicaltrials.gov and extracted information from as many sources as we could to see if we could track down results.

Across PHN trials, diabetic neuropathy trials, and fibromyalgia trials, in general 39 to 44 percent of the trials had results in peer-reviewed literature even several years after the trial was listed as completed. So there's still a mountain of data available that is still not accessible to the general public.

So I'll close there, and thank you very much.

(Applause.)

DR. DWORKIN: So we are only little bit behind. We have one more speaker, and then we'll have about 20 minutes, maybe a little bit more, for questions from you all in the audience.

So our final speaker this morning is Dr. Pamela Horn. She's a lead medical officer in the Division of Anesthesia, Analgesia, and Addiction Products at the FDA. And what Dr. Horn will be doing -- and we thought this would be a valuable springboard in considering the previous presentations and then for the discussion that will follow -- she's going to be providing an overview of recently published guidelines for the use of opioid analgesics in the treatment of patients with chronic non-cancer pain.

As you've already heard, there are some inconsistencies and also some similarities among these different guidelines, and she will be reviewing those for us.

**Presentation – Pam Horn**

DR. PAM HORN: Good morning. I'm going to give you a brief summary of the conclusions

contained in treatment guidelines with respect to the efficacy and effectiveness of opioids for the treatment of chronic non-cancer pain.

My main goal in sharing the conclusions of these guidelines is to compare them in terms of how they defined chronic pain and chronic opioid therapy, what sources they used to reach these conclusions, and where their conclusions have been similar and where they differed in spite of having essentially the same body of evidence available for review.

I have no conflicts to disclose.

The guidelines that are out there for us to review have been published by a variety of professional and government organizations, and there are a lot of them.

So I'm going to limit them; I did limit them in my search to the guidelines that have been published in the past five years, and they had to have articulated some conclusion about the efficacy or effectiveness of opioids for chronic non-cancer pain. Some of the guidelines went straight to the

recommendations for how to manage patients, so those were eliminated.

To identify the guidelines, I used the National Guideline Clearinghouse and limited the search to the past five years. And then if I found that one of the guidelines didn't provide any conclusion about efficacy or effectiveness, I removed it.

This is a summary of the guidelines I'm going to go over this morning. Five of these seven guidelines I identified through the National Guideline Clearinghouse. There are some guidelines that you probably are aware of that didn't come up in the search, and so in discussions with Dr. Rappaport and Dr. Dworkin, I added the Utah guideline and the Canadian guideline for completeness because they identified them as guidelines that are frequently referred to in the field.

The first five guidelines in this table relied on an independent literature review, and the bottom two used other guidelines in drawing their

conclusions about efficacy and effectiveness. Now, the VA guideline did a literature review to make other recommendations in their guideline, but as far as their conclusion about opioid efficacy, they used another guideline.

So the first guideline that I'm going to talk about was published in the Journal of Pain and was commissioned by the American Pain Society and the American Academy of Pain Medicine. In the guideline, the authors defined chronic pain as pain that persists beyond normal healing time, and noted that this has generally been assumed to be about three months.

There was no criteria set on the length of the studies reviewed. Most trials in this review were 12 weeks or less, as we've heard earlier this morning. And from a systematic review, they concluded that opioids are effective for chronic pain, and they qualified this by saying that opioids need to be prescribed to the appropriate patient and that the evidence is limited.

The next guideline that I'm going to talk

about is from the American Society of Interventional Pain Physicians. They define chronic pain as pain beyond the usual course of an acute disease or beyond a reasonable time for an injury to heal, so no actual month or week limit. And the literature review was focused on studies that collected data for at least six months, so much longer than the one we just discussed.

From a review of systematic reviews, they found that there was high-quality evidence of effectiveness, even from these longer studies, but because of the risks of opioids, the recommendation for using opioids was weak.

The next one is the American Society of Anesthesiologists guideline. They define chronic pain as pain of any etiology not directly related to neoplastic involvement associated with a chronic medical condition or extending in duration beyond the expected temporal boundary of tissue injury and normal healing and adversely affecting the function or well-being of the individual. There was no criteria set on the length of the studies they

reviewed.

They did a meta-analysis of trials of extended- or controlled-release opioid therapy, and they concluded that they were effective for periods of up to nine weeks. They reviewed trials of tramadol as well, and they concluded that it was effective, but the level of evidence was not as strong as for extended-release opioids.

They also reviewed observational studies, and they concluded that though the evidence was not as high quality, these studies also showed that various dosage forms of opioids were effective.

The National Opioid Use Guideline Group published the Canadian guideline, and it was based on the results of a meta-analysis of trials. They defined chronic pain as pain that persists for more than six months. There was no criteria set on the length of the studies reviewed.

They concluded that opioids are superior to placebo, and the effect sizes are larger for pain than for function. A small body of evidence indicated that tramadol was effective for pain and

function in fibromyalgia as well.

The next one is the Institute for Clinical Systems Improvement, and this is a nonprofit organization comprised of medical groups in Minnesota and Wisconsin, including the Mayo Clinic. They defined chronic pain as having persisted for six weeks or longer than the anticipated healing time. They concluded that opioids are rarely beneficial for mechanical pain, have never been shown to improve function, and are likely to be effective for neuropathic pain after other therapies have failed.

The most recent Veterans Administration guideline was published in 2010, and it relied on findings contained in the APS/AAPM guideline that I've already gone over. And they adopted their conclusions regarding the efficacy of opioid therapy.

They defined chronic opioid therapy as therapy lasting greater than one month. They concluded that there was a lack of solid evidence of the efficacy of long-term opioid therapy, in

part because the trials were only up to three months long and the lengthier studies were open label and uncontrolled.

The final guideline was done by the Utah Department of Health, and they used other treatment guidelines to formulate conclusions and recommendations. They defined chronic pain as pain lasting more than three months, and concluded that there are safer and more effective therapies for chronic pain than opioids and they should be used first.

So there was a consensus in several of the guidelines that opioids are efficacious for chronic non-cancer pain. That was from the APS/AAPM, the ASA, and the Canadian guidelines. There were also multiple guidelines that pointed out the limitations of the studies, including that the randomized, controlled trials were relatively short, and the studies that collected data for a longer period were of lower quality due to study design.

So the remaining slides I have, I'm going to

highlight some of the differences in the conclusions between the guidelines. The first difference that I'm going to highlight is between the ICSI guideline and the Canadian and ASA guidelines.

The ICSI guideline concluded that opioids are rarely beneficial for mechanical pain; and in contrast, the Canadian guideline found that opioids were effective irrespective of the mechanism of pain. And the ASA guideline found that extended-release opioids were effective for patients with low back pain.

Then there were also some differences in the findings on function. The ICSI guideline concluded that opioids have never been found to improve function, but the Canadian guideline concluded that opioids were more effective than placebo for function, with a small effect size.

So, in conclusion, the guidelines varied in their definition of chronic pain and in the sources they used to form their conclusions. So while there was some variation in the conclusions drawn

regarding efficacy or effectiveness, in general the authors concluded that there is evidence for efficacy or effectiveness of opioids for chronic pain. But the body of evidence is limited by issues like study length and limitations in study design, and the evidence of effectiveness or efficacy does not necessarily mean that opioid therapy for chronic pain is a good option for all patients.

Thank you.

(Applause.)

**Questions and Answers**

DR. DWORKIN: Okay. I'd like to ask the other four speakers to join us on the stage for questions and answers.

Let's figure out the timetable. It's about 10:30, so we are 15 minutes behind the schedule. I think what we'd like to do is go for about 20 minutes of questions to the presenters, and then take a 15-minute coffee break from about 10 to 11:00 to 5 after 11:00.

So this session, the next 20 minutes or so,

is the opportunity for you all to ask questions of the speakers, and there's another thing we're going to do at the end of it. So please, when you come to one of the three mics we have, two in the back and one in the front, please make it clear what the question is and which speaker you would like to answer the question.

Then finally, I'd like to alert our five speakers that I'm going to stop five minutes early to ask them a question that really reflects one of the objectives that we heard Dr. Rappaport and Dr. Woodcock discuss this morning.

I would like five minutes before the coffee break to ask each of our presenters, if they had $15 million to do one research study to address the most important unresolved question about the efficacy or effectiveness of opioid analgesics in chronic non-cancer pain, what would, in two sentences or less, be that study that they would do with the $15 million that Bill Gates would give them?

So I just wanted to alert them that that

question is going to come to each of them in about 15 or 20 minutes. I think it would be interesting. We've seen very lengthy research agendas with multiple, multiple questions, and I think it would be interesting to know, if each of these speakers had money to do one study, what would be their highest priority study.

Okay. Sir, the first question for the speakers.

MALE SPEAKER: Good morning. My question is to Dr. Horn or perhaps Dr. Ballantyne. You can imagine, after reviewing the differences and all the guidelines, how confusing it is for the practicing physician.

One of the issues that are not commonly addressed are the issues of being under the influence, the so-called DUI, driving under the influence. In the recent months, there has been more attention regarding driving fatalities, driving accidents affecting public health, and the effects that patients might have with impairment as a consequence not just of opioids but several other

drugs, but opioids of course will be the poster child of the greatest concern.

What do I do with the patients that I see? And the vast majority of physicians, I don't think, are following the label cautions placed on opioids regarding driving, using machinery, sharp objects, knives, soldiers, law enforcement patients that I have. How should I handle that?

DR. BALLANTYNE: It's true that there's been very little attention paid to it in the guidelines. But I was actually on the panel for the ASA/ASAM guideline development, and we did look at that literature.

The literature suggests that if patients are on stable doses of opiates, then their cognitive function is good enough to drive and operate machinery. That's on a very limited number of studies, but that is more or less how we've gone. And so it's partly to protect cancer patients who are taking opiates and enable them to still be able to drive, if not operate machinery or if not fly planes or drive school buses. I think there's a

difference.

The problem is that that's no longer true if there's a change in dose. So if there's a dose escalation, we really -- and in fact, early evidence would suggest that that's when cognitive function changes and is no longer reliable enough to be able to drive. And we really have no control over what changes in doses are happening when patients are given opiates to take home. So I think it is an important question.

MALE SPEAKER: Yes, sadly --

DR. DWORKIN: We're going to have to limit it to one question for right now.

MALE SPEAKER: It was along the same --

DR. DWORKIN: A very quick follow-up.

MALE SPEAKER: Well, I was just going to say that there has been more recent data -- sadly, I cannot cite it, but there has been data that's suggesting -- in fact, there have been legislation in two states that I'm aware of that are making physicians, as well, liable for prescribing opioids, for instance, to a patient that could be

found or could be charged for driving under the influence.

So there is a big problem here that has not been clearly (inaudible – off mic.)

DR. DWORKIN: Thank you.

Ma'am?

FEMALE SPEAKER: A question for Dr. Turk. Lots of the limitation that you raised are applicable to any RCT in any medical field. And I was wondering if you found the limitation that we see in the opiates trials are about the same or worse than for other medication. And I'm thinking, for example, for psychiatric medication or any other medication that we use in practice. Thank you.

DR. TURK: You're correct. The majority of the concerns that I raised about randomized, controlled trials are generic and could apply to those clinical trials for all types of medication or non-pharmacological treatments.

There's nothing unique about the trial design from the standpoint of the limitations for

the opioid trials. There are some unique characteristics of opioids that have limitation in the trials, but that could be the same when Dr. Rowbotham showed you some of the concerns about the side effects of tricyclics and other things.

So there are some balances that have to occur. But overall, the concerns that I raised about the randomized, controlled trials apply across all interventions and not specific to opioids.

MS. PEPKOWITZ: My name is Rebecca Pepkowitz. I spoke yesterday as a chronic pain sufferer. I think that in my case, I have Ehlers-Danlos, and what we have found is that many people with my condition have extremely, extremely atypical responses, not just to opioids but to many, many medications.

I can tell you, speaking for myself, having gone through 26 surgical procedures and always being given between 30 and 60 opioids subsequently, finding, as Dr. Beth Murinson, the neurologist and the pain management person from Hopkins stated,

three days' efficacy. I get three days of pain relief and then I just start to spin.

If I did not self-police myself and you told me that I could go out and drive while I'm on opioids, you are guilty of allowing me to commit vehicular murder because I can't operate. After three days, the room spins, and if my physician tells me that it's okay for me to go out and drive, thank God I won't, but many people will. And I think it's shameful, absolutely shameful.

Responses, please?

(No response.)

MS. PEPKOWITZ: You can't speak to this issue?

DR. RAJA: I think what you point out is the wide individual variability in the response to opioids. And so I think it behooves every physician or health care provider treating a patient to individualize the care and titrate the medications according to response. And there is --

MS. PEPKOWITZ: I have never had follow-up or titration. After 26 surgeries, I have had

exactly two physicians' offices call me within five days, A, to find out how my pain level was, and B, to ask what my reactions were to the medication. That's two out of 26 doctors.

Most people will say, I'll see you in six weeks or eight weeks. You're good to drive. You're good to go. And when I see them again, they see me for two and a half minutes and tell me they don't have time to listen. Thank you.

DR. DWORKIN: Thank you.

We have a lot of people standing at the microphones, and so in the interest of getting you all to a coffee break, this session, of course, was really focused on efficacy and effectiveness.

So we'd really prefer if your question or comment is not something related to these five presentations and the efficacy and effectiveness of opioid analgesics for chronic non-cancer pain, that you maybe save the comment or question for later today. And that's really in the interest of getting you all some coffee and an opportunity to visit the restrooms.

So ma'am?

MS. NAGLE: Hi. Becky Nagle from ESI. One of the treatments that you haven't talked about with regard to back pain is muscle relaxants, benzodiazepines, and then stimulants to treat the effects. That's a common cocktail that most of these people are taking, and I just wonder what your thoughts are.

DR. DWORKIN: And your question, and who would you like to answer it?

MS. NAGLE: Anyone can answer it.

DR. TURK: I can comment on it. So muscle relaxants, there is a small literature on them. One of the problems with them, just like with many of the compounds, is that they are sedating. And adding those to opioids is definitely going to impair people's ability to function and to drive. Plus, other than just over very short time periods, they don't seem to show that much benefit.

MS. NAGLE: Benzos and stimulants? Any thoughts?

DR. TURK: I'm sorry. Can you speak up? I

really couldn't --

MS. NAGLE: Benzos, benzodiazepines --

DR. TURK: Yes. That does the same --

MS. NAGLE: -- and stimulants.

DR. TURK: And psychostimulant?

MS. NAGLE: Yes.

DR. TURK: So for the benzodiazepines, most of them don't have any direct analgesic activity, and they still add the same burden of cognitive impairments and sedation.

There has been use of drugs like modafinil as a non-amphetamine type of stimulant. And over short periods of time, there seems to be some limited evidence that it might reduce the sedation produced by opioids, but there's not good long-term data on whether or not that's an effective strategy.

MS. NAGLE: Thank you.

MS. VEASLEY: Hi. Chris Veasley with the National Vulvodynia Association and the Chronic Pain Research Alliance. Thank you all for your very articulate presentations. I think it's given

us a quick snapshot of why we're in the clinical mess that we're in right now, and why it makes our job as advocates and yours as medical professionals extremely difficult to educate patients.

In terms of moving forward, my question is, to Dr. Turk and others who would like to respond, what type of research designs -- the top, maybe, two or three -- that you would recommend are the way forward to be able to get us to a point where we can compare these types of medications, study designs, and their effectiveness to lead to evidence-based guidelines?

DR. DWORKIN: Yes. Chris, we're going to get to that as soon as we -- well, actually, in about 5 or 10 minutes. We're going to ask each of them to answer your question.

Jas?

DR. SINGH: Jasvinder Singh, University of Alabama at Birmingham. This question is for Dr. Turk and Dr. Raja.

You alluded to the fact that with very few number of studies, usually if a systematic review

or different systematic reviews include those estimates, you'd probably get similar estimates because the number of patients are being captured similarly in different systematic reviews.

Where the variability is coming from is from these 49 different quality assessment scales and the people who are assessing quality of those scales in systematic reviews.

The question is whether, when you look at the Cochrane systematic reviews that recommends one or two scales and have been more systematic, whether you found less variability in use of scales in Cochrane versus non-Cochrane? And if not, or if yes, what is your recommendation for going forward how we can harmonize reporting of quality across systematic reviews? Thank you.

DR. TURK: I wish I could say thank you for that question because I'm not sure I have a good answer for it.

The problem with having multiple criteria out there is that it makes it very difficult to compare reviews across meta-analyses. There needs

to be some effort, number one, to reduce the number of those, and two, to see if we can't come to some harmonization among what the key variables or key factors need to be in those particular studies.

To my knowledge, there haven't been any head-to-head across one of those selection criteria. But selection criteria, remember, is only one of the characteristics that goes into some of the differences that we're seeing. There's also a range of other factors that contribute to how people make decisions about what to include, whether they include published or non-published trials. There's a whole range of factors.

So those 49 criteria for quality, that's just one of the factors that we need to harmonize. But we also need to come up with some standard ways that we think about how we're going to gather information, how we're going to include information along the same way.

So there's definitely a need for that. But right now, for the average consumer of this literature, it is very difficult to draw any firm

conclusions when you see inconsistencies.

DR. DWORKIN: We have six people standing at the microphones. So please, let's not have any additional people go to the microphones, in the interest of having a break before lunch.

Charles, you're next.

DR. ARGOFF: Charles Argoff, Albany Medical College. It's for anybody.

I don't mean to make things more complicated. However, we're speaking about chronic non-cancer pain. There's differences in the literature about what is chronic, three months, six months, fine. But we are kind of avoiding a very important subject as well, in my opinion -- I'd like to know what your thoughts are -- about cancer pain. What is cancer pain? What is cancer pain?

It's my knowledge there are now studies -- there are drugs that have been improved on the basis of breakthrough cancer pain in people who were included in that study population who hadn't had active cancer for over a decade, who were being treated for pain that was -- how was

that defined? How was the FDA looking at proving that the pain is cancer-related? And when people are surviving more and more and more cancer-free, when does it become non-cancer pain, and how do we use that information to look at the big picture?

DR. RAJA: Charles, I think you raise a very important point in the sense that traditionally we looked at cancer pain as pain in any patient who's had cancer, whether it be either from the disease itself or from therapies associated with the disease.

But as you have indicated, we're seeing more and more patients in who the original cancer has been adequately treated, and either they are in remission or on a stable course for long periods of time, and their pain still persists. And what is the etiology of their pain at this stage?

So rather than labeling them as cancer pain, maybe we should be looking at what is the mechanism of pain in these patients and what is contributing to their continued pain, and are opioids appropriate in these patients?

Unfortunately, there are very few randomized trials or evidence to say, are opioids or even other drugs appropriate in this class of patients. And we're left with empirically treating these patients rather than based on, really, clinical evidence.

DR. ARGOFF: Thank you.

DR. DWORKIN: Ken?

DR. SOMMERVILLE: Hi. Ken Sommerville from Pfizer. Thanks for the great lectures to all of you.

Dr. Ballantyne, that cohort of patients who are taking high-dose opioids over a long term and not responding, has there ever been any work or any evidence that if they were taken off the opioids for sort of a drug holiday, that they might have a better response at a lower dose if rechallenged?

DR. BALLANTYNE: Well, I did show some reports, so there are reports of patients who come off who -- and I think what's surprising is that once you get them through a taper, yes, they seem to have reduced pain.

The problem is that for patients who've been on opioids for years, even if you successfully get them through an intensive rehab program, get them off, and get them much better, and you can get them much better, some of them will relapse.

We already have that experience, that quite a lot of them actually do relapse. In other words -- in fact, there's a study that was published recently that shows that only 10 percent of patients who go through a program and come off opioids actually stay off opioids. So it's a problem and it's related to how long they've been on.

So for people who haven't been on for very long, then tapering is successful and it's sustained. But for people who've been on for years, it's not the same. It's much more difficult.

DR. SOMMERVILLE: Thank you.

DR. DWORKIN: Ma'am?

MS. STEINBERG: Hi. Cindy Steinberg. Thanks very much for your presentations.

Has anyone looked at retrospective or community societal studies of people that have been on long-term opioid treatment? There are many people out there that have for many years. I, for example, run a number of support groups. I've had 250 people come through my group, And many of these people have been on opioids long term.

Why don't we look at that population already and see why it has helped some people and why it hasn't? We have examples of that.

DR. BALLANTYNE: Well, I think there are certainly plenty of anecdotal reports of people who are on high doses of opiates and are doing just fine, according to these reports. And that's certainly been our belief for a long time.

In the state of Washington -- I don't think it came up very much during this meeting. But there is an initiative in the state of Washington -- in fact, there's a rule or a law -- that's trying to control the high doses. And people are beginning to taper patients.

When you start trying to taper these

patients, that's when you see that they really are dependent and that the dependence is a very hard thing to overcome. Whether or not it's a good thing to taper these patients, I don't know. They certainly looked a lot better before they were tapered than they do during the taper, you know. The taper is really difficult.

So I think it's easy to believe that high-dose patients -- and we certainly know from addiction experience that people can be maintained on opioids and function really well, function in society, the workplace, on high-dose opiates that are kept at stable levels. But they're not pain patients. They're different.

MS. STEINBERG: Yes. I'm actually talking about pain patients. And when you say high dose, I'm not sure exactly what you mean. But I know many people that have been on long, stable doses, myself included, for a very, very long period of time, have not changed the dose, have not increased the dose, have only had a positive effect from it.

DR. BALLANTYNE: Well, I'll just say that I

just actually appreciate that. I understand that there are people who do well. And the reason that we started tapering is just on safety. It's on the evidence that we now have that high doses can be quite dangerous to people.

But all of that's across a population. That's not speaking to individuals. There may be individuals who do well. But if you look at the population, the evidence on the lack of safety of high doses is quite compelling. And there are certainly a lot of deaths associated with high doses.

MS. STEINBERG: Fine. Again, I just wanted --

DR. DWORKIN: Thank you. We really --

MS. STEINBERG: Okay. Sure.

DR. DWORKIN: Sir?

DR. SILVER: Thank you very much. I'm Dr. Harris Silver. I'm a drug policy analyst and advocate. And this is actually to Dr. Raja, Ballantyne, or Turk, if either one of you respond to this statement. And tell me if it's true or

false. It's about addiction as a side effect, which to me is a misnomer because it's actually a comorbidity that's potentially deadly.

DR. DWORKIN: I'm sorry. This panel is on efficacy and effectiveness.

DR. SILVER: Well, they talked about side effects. That's why I --

DR. DWORKIN: I know. But I'm --

DR. SILVER: And we've just been talking about it.

DR. DWORKIN: I'm just trying to get you all to a coffee break, and I also want to ask the panelists about a research agenda. But I think later in the day, there will certainly be time for your question. I think, at this point in time, to start talking about addiction is going to mean we don't get the coffee. I think we're all happy to kill the coffee break, but --

DR. SILVER: Well, I just wanted to find out how we know people are addicted in these studies.

DR. DWORKIN: Let me personally say that's a difficult question and --

DR. SILVER: -- which impacts the results of the studies.

DR. DWORKIN: Do either of the other two of you at the microphones have a question about efficacy, effectiveness of opioid analgesics? I'm sorry, but we -- yes, please.

MS. KELLY: Kathleen Kelly from Janssen.

This really goes across the panelists because many of you touched on this. There's differing data on the correlation or lack of correlation between relief of pain and improvement in function.

Is there a phenotype, a dose, a duration, that would sort of characterize the patients who get both and the patients who seem to have a relief of pain but no increase in function? This is obviously very important to patients as well as to society. Thank you.

DR. RAJA: I'm not aware of any study that has carefully looked at -- within subjects, that is -- in a given subject, is the reduction in pain associated with improvement in function. Most of

them have been group data.

There are studies prospective studies, one of which we did, that looking at chronic opioid, 12-week periods of transdermal fentanyl, and looked at their reduction in pain as well as improvement in function using objective measures such as an active watch, such as activity monitor. In that, overall as a group, we found that reduction in pain was associated with improvement in function.

But when we looked within subjects, there were two subsets of patients, one group of patients where the reduction in pain was associated with a marked improvement in function as well. However, there was a subset of patients who, because of sedation associated with the drug, had a reduction in function while pain intensity reduced.

So I think it's a subject-to-subject variation in this relationship between reduction in intensity and improvement in function that needs to be investigated further.

DR. DWORKIN: And the last question before the coffee break.

MS. REED-HOLTUM: Thank you. I'm Lexi Reed-Holtum with the Steve Rummler Memorial Foundation. My question is about -- and I hope this meets your criteria; I think it does -- is about evidence-based information that we have.

If we do know, which is true, that the rates of prescription matches the rates of increase in overdose and death, and we know, and there's evidence out there that states that this is now the number one cause of injury death in our country today -- if we have all this evidence, what exactly -- and this question is really for Janet Woodcock. But what more do we need in terms of evidence that this is dangerous?

So anyone can feel free to answer. And also placebo, in my opinion, if someone's in pain and you're doing a clinical study, how effective is it really if you're not giving someone any kind of anything, and then you're giving them opioids and comparing the two and saying that it's effective?

DR. DWORKIN: Well, I think your first question very similar to the question that I want

to ask each of the speakers to address.

So why don't we combine your first question and my question, because we're only allowing you all one question apiece, and now turn to asking the five people on the podium if they could -- if they had about $15 million, which is, I think, a reasonable sum for a kind of important study with hopefully compelling conclusions.

If you had about $15 million to do one research study, what would be your choice, in three or four sentences, to address some of the really unresolved questions we've heard about this morning? What kind of study would provide important information that could move things forward?

Raj?

DR. RAJA: That's the problem with sitting on the left end of the table.

(Laughter.)

DR. RAJA: Although the gold standard is randomized, controlled trials, I think the $15 million study, in my opinion, is probably not

going to be a randomized, controlled trial.

The two critical questions, I think, to be answered are, what is the long-term efficacy of opioids in patients with chronic non-cancer pain? And are there appropriate predictors of which patients are those patients, subset of patients, who are likely to be the most benefitted from this long-term treatment?

So the study design that I would like to see is a group of well-characterized patients, including patients with chronic osteoarthritis or low back pain and chronic neuropathic pain, patients who are characterized, as we heard yesterday, using quantitative sensory testing and other measures in terms of their mechanisms of pain; and then followed by therapy with opioids over a period of at least a year.

Then examining what proportion of these patients at the end of that period are still continuing on opioids. What is the overall efficacy in that group of patients? What are the other side effects associated in these patients?

But in particular, are there a subset of patients, based on their mechanism, who were more responsive to the opioids than others?

DR. DWORKIN: So at least one year in duration, open label cohort study with extensive baseline characterization of the patients.

Jane?

DR. BALLANTYNE: Well, I think that we're probably all going to say we've got to identify the patients that do badly versus the ones that do well. What I would spend $15 million on is, in this era of the electronic medical record, making sure that within my record, which has a wealth of data that I can look at, mine, is that there is some record of patient-reported outcomes so that we introduce systems so that patients can tell us what we need to know is, how is their pain, how is their function, and how do they rate their quality of life?

But probably most importantly, since no one can agree what is the desired outcome of pain treatment, as Dr. Turk was saying, is have they

achieved their personal goals for the treatment?

So one thing that we're doing at UW is using a tool that actually starts out with, what is my goal for treatment? And then follows the patients over years, as has this treatment, or has any other treatment, or has any combination of treatment, actually achieved the patient's goal for treatment?

So I would spend a lot of money making sure that in the electronic medical record, I have some sort of measure of how the patient is doing and not just the surrogate measures that we have at the moment.

DR. DWORKIN: Dennis?

DR. TURK: Well, I wish I had the $15 million. I'm not sure whether that would be enough. But I think I would like to build off of what Raj was suggesting, although he suggested QST. But I would suggest that there are a range of potential factors that are important to be considering; that is, all the literature suggests that there are a subset of patients who get some benefit and able to function reasonably well. We

don't know much about what those individuals are.

So I would go along with the one-year trial, well-characterizing patients, identifying, if we could, responders and seeing if we could identify what are the characteristics of responders so we get to the point in which we might be able to prescribe patients based on relevant characteristics.

My only other modification, if I could find a way to squeeze this in, since in clinical practice, rarely are patients treated with one medication; and therefore, to find some way to look a combinations of medications, which is why I think the $15 million is not going to be enough.

But if we really want to understand what's happening in the real world of patient care, at least for chronic pain, we almost never see a patient who's taking one medication. So therefore, we need to know much more about the combinations of medications and how those are going to interact with characteristics of patients and the mechanisms.

DR. DWORKIN: Mike?

DR. ROWBOTHAM: So the goal would be to get at least a thousand patients into a trial. You'd want to have well-characterized pain disorders, at least ones that you could diagnose with some confidence.

The study would need to be randomized, and to really put everything into context, you'd need to randomly assign people to get either an opioid or a non-opioid. And probably the most practical design would be to have three or four medications that you are randomizing between. And if patients decided they didn't like one, they just went on to the next one in the sequence. And then as part of your assessments, you would do not only patient-reported outcomes, but you'd do some standardized tests, especially things like driving tests, to see how good their function is in a standardized environment.

DR. DWORKIN: And this is placebo-controlled?

DR. ROWBOTHAM: No. No. I would do it

without a placebo, and patients would be randomized, and you would have a regimen that they would go through that included opioid to non-opioids. Because there's so little data, trying to see if the alternatives to opioids are as good as the opioids. There's really just a couple of studies in the literature.

DR. DWORKIN: Pam?

DR. PAM HORN: Well, one of the most troubling things to me is that it seems like the efficacy that we see in trials, there's a big gap between that and the effectiveness that we see in clinical practice.

So I'd be interested in whether there is a model that could be developed for primary care physicians, assuming that they are the ones who are doing most of the prescribing of opioids, where they can take the best practices that we know about in prescribing opioids, and whether it can translate into better benefit for their patients.

DR. DWORKIN: Okay. I's five after 11:00. This is now time for the coffee break. And why

don't we all reconvene here in 10 to 15 minutes, absolutely no later than 11:20, when we will begin.

(Whereupon, a recess was taken.)

DR. DWORKIN: We're going to be restarting, so if all of you can take your seats.

So we're going to start soon. Let's get everybody up on the podium, not only the speakers from this morning from before the coffee break, and also the panelists who are going to be giving presentations.

That should make things more efficient because there won't be a constant up and down. And there are going to be no slides for this session, so we won't have to worry about seeing slides.

(Pause.)

DR. DWORKIN: We are missing a few people that are supposed to be up on the podium, but we will start anyway.

The next session is five five-minute discussions of this morning's presentations. That will be followed by a continuation of questions and answers and also a discussion amongst the

panelists. And then we will try our best to adhere to the lunch break scheduled for 12:30. So that gives us an hour and five minutes; that should be enough time for the panel discussions and the open discussion.

So it's a great pleasure to introduce our first discussant, Dr. Rollin Gallagher. He is currently deputy national program director for pain management in the Veterans Health System. He's also the editor-in-chief of Pain Medicine, and has been for about 10 years. And he's a former president of the American Academy of Pain Medicine.

**Presentation – Rollin Gallagher**

DR. GALLAGHER: Thank you, Bob, and thanks, FDA and others, for organizing this great conference.

How can you comment on such marvelous, superb presentations? I mean, there's really not much else to say except for "Amen" to all the questions. But I'm going to focus a little bit, based on my biases, as a policy person, provider, and researcher in a large, capitated health system,

the VA Health System, and now working with the DOD to develop a common step-care model for chronic pain in our population of patients.

Don't forget that over 55 percent of incoming veterans from the present conflicts, or at least the immediately past conflicts, have chronic pain disorders. And not only that, but, as you know, many of them have been grievously injured, with one or more limb amputations, multiple wounds, and then the psychological scars of battle and, of course, neurological trauma from blast injuries.

So we're dealing with incredibly complex patients, which I think points to the need for being real-world when we start developing our treatment algorithms for chronic pain and looking at the needs for studies that address this complexity, whether it's in a veteran coming back from war with PTSD and several different causes or injuries that cause pain, but also a worker, and industrial worker or someone else, who develops a low back disorder and then can't work very well, or develops a depression, or has a family trauma,

divorce or something, and the effects of that on how they respond to medications.

So complexity management and addressing a complexity is really a key here.

One of the things that we're doing to try to reduce risk is to look at a patient-centered approach in the VA, and that is really educating the patients and giving them a choice based on informed consent.

Informed consent is something we assume when we start a medication or a clinical trial, certainly. But informed consent really gives the patient -- and I'm talking about written informed consent, a very formal process -- gives the patient all the information they had to make a decision as to whether they want to try opioids for pain.

I want to reflect again to Doug [sic] Rowbotham's presentation, where he listed all the other treatments that are really the standard of treatment now for pain, not just medications. And the question I would ask the distinguished panel here is how can we design studies -- I think

everybody has alluded to this, or many of the speakers have alluded to this -- how can we design studies that address a higher standard of care along with the medications?

This reminds me of anxiety studies in the mid '80s, when the NIMH would not fund anti-anxiety medication studies unless there was a standardized cognitive behavioral treatment approach as part of treatment for everybody, and then the medication effects were looked on top of that, or the medications were compared, placebo versus active drug, or active placebo versus investigational drug.

So they started off with what was a standard of care, anxiety control training, and then added on the medication trial on top of that. And I think that's what we need in chronic pain treatment studies, because the experts and all the people around the table, we all know -- and Dennis Turk and I, for example, coming from a pain rehabilitation background, where you put together intensive, high-quality, multimodal treatment

approaches to get people back to work. And it worked, and we had good studies of that. But we haven't had a clinical trial of that kind of study.

So a former nurse colleague of mine suggested to me at the break that why don't we multiply that $15 million by 5 and do the big clinical trial that will then enable us to prove that complex pain responds best to multimodal integrated biopsychosocial treatment interventions.

A couple of key points I want to mention. First of all -- and I'd like to compliment Jane on her terrific presentation and review of the literature in this area. But her case, her patient, pointed out, I think, the real issues we're dealing with here.

The opioids helped her stay at her job initially, and then she had a life event that may have caused her a depression, may have caused her to lose self-esteem, autonomy, financial independence, et cetera.

If the depression had been treated -- in other words, if we had been following her

longitudinally -- would we be able to find out whether antidepressants would treat her depression, she could lower her dose of opioids and actually get effect again and go back to work.

These are the kinds of questions that we need to be able to answer if we're going to be successful in teasing out this puzzle of chronic pain and opioids and how to treat our patients more effectively.

So again, I applaud the FDA for their work in developing this panel, and I look forward to coming up with some solutions, and the $75 million that we need for that study. Thank you.

DR. DWORKIN: We'll take questions later about where the $75 million is going to come from.

(Laughter.)

DR. DWORKIN: Though if any of you are philanthropists, come see one of us during lunch.

Our next panel discussant is Dr. Mark Hochberg. He's head of the Division of Rheumatology and Clinical Immunology at University of Maryland School of Medicine. He's also the

editor-in-chief of Seminars in Arthritis and Rheumatism.

He's published almost 500 articles and book chapters focusing on the clinical epidemiology of musculoskeletal disorders. And it's a great pleasure to have him here.

**Presentation – Mark Hochberg**

DR. HOCHBERG: Thank you very much, Bob. I will certainly keep to time.

I've been in the academic practice of rheumatology for about 35 years, and I actually see patients like the one who was briefly presented this morning with the name of Jane. So my comment about her would have been that I think she now has a chronic widespread pain syndrome, previously called fibromyalgia. I usually don't use the term "fibromyalgia" with my patients, but actually adopt the new CWP description.

So let me comment on what I had reviewed previously from the slides that were provided to me for this morning. And I want to start with a quote, which I think summarizes some of our

concerns about long-term opioid therapy for chronic non-cancer pain here. Dr. Rappaport may remember this from one of the FDA Arthritis Advisory Committee meetings that he participated in, although he goes to a lot more of those than I do.

This was a quote from the patient representative on the panel that, "Patients don't fail drugs; drugs fail patients." And I think that's what we're dealing with here in terms of long-term opioid therapy for our patients who either don't have efficacy in the first place; don't achieve a patient-acceptable symptom state, which I'll come back to; or patients who have intolerable adverse events; or patients who initially respond, but then go through the process that was so nicely described this morning of dose escalation, where they then develop a tolerance, dependence, and further adverse events, and really become the patients who were summarized in some of the epidemiologic data yesterday of those who are on greater than 50 MED, who have worse physical function than those who are on lower doses.

So I approach this I guess from the standpoint of osteoarthritis, where I've done most of my clinical research and participated in the development of recommendations.

We heard about the different types of pain. OA pain has been considered to be primarily nociceptive. We now know from recent studies that it's not all nociceptive pain, that about one-third of patients with osteoarthritis will have central, non-neuropathic pain, which was referred to early this morning as so-called dysfunctional pain. And that may be why agents which are efficacious for nociceptive pain are not effective in all patients with OA.

I think, based on Dr. Raja's presentation, efficacy of short-term opioid therapy for osteoarthritis pain is a given. From placebo-controlled trials lasting less than or equal to 13 weeks in duration, summarized in this Cochrane review that he cited recently, we know that opioids work.

So where do we use opioids in the management

of osteoarthritis? And you know that we're not allowed to have slides, and I think I circumvented that a little bit by sending one in and asking that it be reprinted as part of your handouts.

I recognize that you have very limited handout material here, but you do have one figure which you might look at as I speak now for the next two minutes which I think I have left.

So Dr. Rowbotham was the only presenter who talked about the non-pharmacologic approaches to pain management and how that might fit in or be compared with opioid therapy. And that's really the cornerstone of treatment for people with chronic pain due to osteoarthritis, and I would think due to other musculoskeletal disorders.

So we need to think about this multimodal approach, which was just mentioned, to pain because all patients who are treated are really getting a multimodal approach, and we don't study the multimodal approach in clinical trials.

So what we do in clinical trials is really to determine the efficacy and safety or

tolerability of an agent, and then how we use it in practice is very different, as was cited by Dr. Turk this morning, from the clinical trial world.

He brought up a very good point, I think, which is the difference between clinical and statistical significance. In the data that you showed about the efficacy of opioids compared with placebo for musculoskeletal pain, there was statistical significance, but the delta between the improvement in pain with an opioid versus the improvement in pain with placebo was less than 1 unit on a 10-unit numerical rating scale, or less than 10 points on a 100-unit visual analog scale, which is considered to fall below the minimal clinically important difference in osteoarthritis.

Now, granted, we shouldn't use the MCID for group data; it's really developed for individual data. But the size of the effect is, in fact, similar to that which we see with other agents that we use for pain, including nonsteroidal anti-inflammatory drugs, which haven't been mentioned at all, either as potential comparators

or as something which people fail to respond to adequately, because the drugs don't work in everybody, prior to their getting opioid therapy.

So what we really need to look at are these other patient-reported outcomes that have been used, and the Osteoarthritis Research Society has developed responder criteria which utilize improvement in pain, improvement in function, and improvement in patient global assessment, similar to what impact is developed for their moderate and substantial improvement. There are things called having minimal clinically important improvement, achieving a patient-acceptable symptom state.

Then I think the other issue for this $15 million study, which we would love to compete for at the University of Maryland, particularly with regard to our integrative medicine program, is what are the satisfactory active comparators for opioid therapy, given that we shouldn't compare it to placebo in these patients?

This is where we -- we, being the American College of Rheumatology -- and I don't look to

speak for the ACR here; Dr. Borenstein in the audience may do that if he has the opportunity later. But the ACR in its recent recommendations for the management of osteoarthritis really placed the use of long-term opioid therapy in a very limited setting, in patients who are either unwilling to undergo or have medical contraindications to total joint arthroplasty for their hip OA or knee OA because we recognize the efficacy of surgical interventions in the vast majority of patients, and think that opioids should be reserved for those patients who either don't undergo the surgery because they're not willing to or have contraindications to the procedure.

So thank you for your time.

DR. DWORKIN: Our next panelist is Dr. Susan Horn, who is senior scientist at the Institute for Clinical Outcomes Research, and vice president of research at the International Severity Information Systems, Incorporated in Salt Lake City.

She's also adjunct professor in the Departments of Biomedical Informatics and PM&R at

the University of Utah School of Medicine. She's been the principal investigator of more than 30 practice-based evidence guidelines. And it's a pleasure to have you here, Susan.

**Presentation – Susan Horn**

DR. SUSAN HORN: Good morning. In order to address the many issues raised yesterday, both on long-term care use and patient differences that the public speakers talked about as well as my colleagues this morning, we have been developing a chronic pain registry of patients in routine clinical care who have chronic pain.

We've based it on a practice-based evidence study design, which is an observational study design that we've used in many other clinical areas in the past to discover the relative contribution of specific interventions, both individually and in combinations, to patient outcomes, taking into account patient differences, severity of illness, and other relevant factors.

In this database, this chronic pain database registry we've put together, both the patients as

well as the front-line providers record standardized data elements as part of standard of care. So everybody is part of this database. We don't need a consent process to get them to be participating.

Then what we do is we don't consider this an add-on effort -- it's part of the regular medical record -- and are able to pick up information about diagnosis, severity of illness, all of the medications that people are taking, all of the other interventions that they're receiving, and validated outcome measures, recorded all in an electronic database.

So this chronic pain registry that we've put together is capturing longitudinal as well as ongoing patient characteristics for both patients who have had cancer in the past and non-cancer patients -- as I say, all their treatments -- and both their pain and functional outcomes. And this is from real-world patients with chronic pain. The registry has also been designed to identify genomic factors associated with established phenotype

characteristics and disparities in treatment.

We've begun analyzing this database at present to identify those patients characteristics and interventions, both drug and non-drug, for chronic pain management that is associated with these better long-term outcomes and fewer harms, such as adverse effects and opioid-related aberrant behaviors that we've heard mentioned.

We're also analyzing two additional questions. One is why patients discontinue pain treatments, and a second is what beneficial treatments are of lower cost to the health care system.

So this registry is beginning to provide the information necessary to develop the evidence base required to realize personalized analgesic prescribing, to inform preclinical analgesic drug development of new therapeutic targets, and to facilitate the enrichment of patient selection for analgesic efficacy trials.

Specifically, it can address the following issues that we've been discussing:

First of all, data available from real-world patients on the use of all types of analgesics in the treatment of chronic pain;

Secondly, to determine the populations and individuals who would benefit from chronic use of analgesic or non-analgesic therapies in the treatment of chronic pain;

Also, the characteristics of individuals with chronic pain, who are at higher risk of adverse events for both drug and non-drug treatments of chronic pain;

Then, also, what are effective alternatives to the use of opioid analgesics in the treatment of chronic pain.

We're looking forward to further questions from you and further future analyses as this database continues to grow, which as of today has over a thousand patients in it, followed for a several years period of time, where we're going to be able to look at many of the interesting questions you have been raising. Thank you.

(Applause.)

DR. DWORKIN: Our next discussant is Dr. Frank Porreca. He's a professor in the Department of Pharmacology at the University of Arizona College of Medicine. He's received the CARE Aware for basic science research from the American Pain Society, and he's the editor-in-chief of Life Sciences.

**Presentation – Frank Porreca**

DR. PORRECA: All right. Well, thank you, Bob. So Dr. Rappaport invited me to comment here as a basic scientist, so I'm going to come at this from a little bit of a different point of view based on the comments that were made this morning.

This meeting was initiated by a series of wonderful lectures that really focused on the basic science that was related to chronic pain, to different aspects of chronic pain. And it seems to me that the fundamental issue is to have a good understanding of the impact of pain on the brain. So I just wanted to bring it back to the issue of trying to make decisions where we have really limited information.

So one of the things that I just want to remind everybody of is the fact that chronic pain seems to have a dramatic effect on the brain itself. And we saw some data that were presented by some of our speakers. Sean Mackey showed some beautiful imaging data that shows the impact of chronic pain on the brain, and there's a number of emerging studies that seem to confirm this, both on the preclinical side and in experimental models and in humans. And the fact that this results in numerous changes in patients with changes in cognitive function and decision making.

So what we have to appreciate when we consider whether or not opiates and opiate use for the treatment of chronic non-malignant pain is appropriate is that we do need to have an increased understanding of how opiates act in a brain that has been altered by chronic pain.

So circuits are different in chronic pain conditions, and we know that the actions of opiates in terms of what they do, both in terms of their efficacy and in terms of their side effects, can be

and will be markedly different.

So the basic science data support the idea that opiates are effective. In preclinical models of chronic pain, animals with injuries that we think are representative of the kinds of circumstances that lead to chronic pain, those animals will self-administer opiates, and do so in a pattern that's extraordinarily different from animals without injuries.

So animals with injuries will self-administer opiates at a rate and with a schedule that is consistent with pain relief and not with abuse. And so this is really quite an important observation to me. If one gives a pain-relieving therapy along with an opiate, animals will self-administer for less opiate, to say they will diminish their self-administration for opiates.

The reason this I think is quite relevant is that, again, the circuits on which opiates act in the setting of pain are dramatically different. So related to this, it is also well-established in the preclinical literature, although much more work

needs to be done, that the rewarding actions of opiates are diminished in the setting of chronic pain.

So this can be studied and evaluated by direct evaluation of the changes that are occurring in the reward circuits, and we do know that animals will have a diminished reward in the setting of chronic pain.

So the reason for emphasizing this is that relief of pain and activation of reward pathways that might be associated with addictive properties of opioids may be separable, and are likely to be separated on a basis of the neurobiology that is actually engaged in the setting of chronic pain.

So we don't know what the clinical window is, and we don't know what the effects of opioid treatment in the long term are. And certainly these are key factors, and I think it speaks to our lack of understanding of neurobiology in the setting of chronic pain.

I just want to end by going back to an observation, that we do have drugs that are used in

the treatment of chronic pain, and Dr. Rowbotham mentioned a number of these this morning. And I just want to remind everyone, really, that these drugs are actually not very effective in the treatment of acute pain, acute nociceptive pain, postoperative pain. So the drugs become more effective in the setting of chronic pain. And this, again, really speaks to the changes in the neurobiology that are occurring in the setting of chronic pain.

The point is that those drugs that are used -- the gabapentinoids, for example, and the reuptake inhibitors -- are not addictive drugs. They are effective; they are somewhat effective. They have numbers needed to treat that change from 11 in the case of gabapentinoids in acute postoperative pain to somewhere between 4 and 6 in neuropathic conditions.

So there is something that is fundamentally different in the setting of chronic pain. The point is, of course, those NNTs show that they're not really wonderful drugs. We have to treat a

number of patients before we get efficacy. But again, pain relief and addiction are separable and are likely to be separable neurobiologically. And I think that that is really, again, demonstrated by the fact that we have drugs that seem to separate that.

So the last point I would make is simply the one that was brought up by Dr. Woodcock this morning when she opioid the session. And she pointed out that evaluation of the use of opioids in chronic non-malignant pain has to be considered within the context of the other available therapies.

She has written about other approaches. So we need to understand the neurobiology of the chronic pain condition much, much better, and we need to have other approaches that can lead us to improving the drugs that are not addictive; the Holy Grail of pain research is to create and to discover non-addictive pain medications.

I think the data are starting to show that that is biologically possible because I don't think

we really knew that, and perhaps we still don't know that for a fact. But it is potentially possible. And Dr. Woodcock has called for novel chemistry, novel strategies by functional molecules, multiple activities.

I think these and other ideas need to be vigorously explored so that we can create drugs that have increased efficacy for the treatment of pain with much, much better NNTs than the ones that we currently have, and that don't have the addictive burden.

So I think opiates confuse us because they are pain-relieving and they are addictive. These may not necessarily be the same neurobiological processes. And I think we need to focus on the important aspects, which is to identify the mechanisms of pain relief in the setting of chronic pain by understanding the neurobiology and by increasing our efforts in chemistry. Thank you.

DR. DWORKIN: Our final discussant is Dr. David Simpson. He's professor of neurology and director of the Neuromuscular Division at Mount

Sinai Medical Center and School of Medicine.

David's renowned for his expertise in HIV neuropathy. He has over 200 publications, and he's on the editorial boards of several journals, focusing on AIDS, HIV, and neurology in general. So it's a pleasure to have him wrap this all up for us.

**Presentation – David Simpson**

DR. SIMPSON: Well, thank you very much to both Bobs for having me.

I'd like to use my few minutes as a discussant to jump from some of the points raised by the speakers and questioners, expand on them, and perhaps engender further discussion and perhaps even a bit of controversy. And I'd like to make three points.

The first one, actually, was raised by Charles Argoff in the question period earlier, and it's definitional. It relates to the issue of cancer versus non-cancer. And this has crucial impact on not only labeling of current drugs, such as the ultra-rapid-acting opioids, but we've heard

some impassioned discussion yesterday from some of the speakers on a plea for changing labeling of opioids, perhaps following these same approaches.

Now, there's been much written about this. Russ Portenoy and others have done so. And I think it's fair to argue that cancer-related pain is an enigma which is not well-understood by clinicians. Historically, I think the notion probably related to the fact of rapidly progressive disease, fatal, perhaps with more tolerance of risk, I would argue that notion is currently inaccurate and probably obsolete.

In my 30 years of working with AIDS patients, there's I think a very important analogy. That used to be a disease that killed people within six months to a year. Now people have long life spans. And I think much can be said about cancer today as well.

Is cancer-related chemotherapy any different from antiretroviral chemotherapy neuropathy? Clinically, mechanistically, and otherwise, I think that's a difficult argument to make. So before we

rush into labeling changes and the like, let's all be clear on the definition of the disease we're talking about.

The second point I'd like to make, and I think Mike Rowbotham and Dennis Turk raised this issue as well, is publication bias and impact on publications, whether it be reviews, meta-analyses, and guidelines. Dennis pointed out nicely that there are over 49 different algorithmic approaches to how one rates evidence in the literature. And, in fact, I've been a user of one of those algorithms as a chair of the quality standards subcommittee of the American Academy of Neurology, publishing guidelines on botulinum toxin for many therapeutic uses, including pain.

One of the limitations of these guideline algorithms is that, at least in the American Academy of Neurology and many others, we're limited to fully published studies, virtually ignoring abstracts or registered results in clinicaltrials.gov. And the reason for that, of course, is without the methodology of the trials,

how does one rate the evidence? This is only partial data sets.

However, by definition, these reviews, meta-analyses, and guidelines will be biased toward published studies, toward positive studies, and negating many of the negative results.

I don't know the right solution to this. It is a difficult problem. The registries are trying to deal with them, but certainly we need to go much further in improving our methodology of how these guidelines are generated.

Now, the third and final point I'd like to make relates to what Dennis mentioned in the beginning of his talk, which is the huge gap between evidence and practice. And as a clinician as well as a clinical investigator and the guidelines' author, I am acutely aware of the difficulty in caring for patients in the office with the paucity of evidence that we have in many of the diseases we treat.

As an example, HIV neuropathy Bob mentioned I deal quite a bit with. If I used literature-

based evidence or FDA approval for the drugs that are used to treat my painful HIV neuropathy patients, I would have to tell them, "I have nothing to treat you with because we don't have evidence nor an FDA-approved agent." Does anybody in the room think that's proper medical care? I doubt it.

So I think we must be very, very cautious in using lack of evidence as a strict guideline as to how to practice medicine. And if I would ask Bob Rappaport or the FDA officials this question, I suspect that they would agree with me, one has to treat with something, even in the absence of data.

The other point I would make relating to this issue is we need to be careful about double standards. When we talk about the lack of data for chronic opioid use and chronic pain conditions, do we use those same standards when we talk about drugs like antidepressants and anticonvulsants and drugs that clinicians use for months to years?

Those trials are of the same short duration as we have for most of our opioid studies. The

placebo-controlled periods go from 8 to 12 weeks, yet clinicians use them for months to years. Clearly, we need data. We need better research. We need to answer these questions with all those millions of dollars that Bob is offering us.

However, my final point I would make is that we can't confuse two major agendas on the table. One is, what are the research priorities for unanswered questions? But separate is, what do we do today to help our clinicians treat their patients both in terms of FDA regulations, guidelines, and best practice?

Those are separate agendas. We must be careful not to confuse them. Thank you.

(Applause.)

**Full Panel Discussion**

DR. DWORKIN: Okay. It's noon, and so we have a half-hour before the lunch break. What I'd like to do is spend the first 10 minutes of it allowing the speakers and the discussants to ask questions among themselves.

So let's have a 10-minute discussion where

any of you who have questions for each other get a chance to ask those questions, and then we'll open it up to questions from the audience.

Speakers, panelists, any comments on each other's presentations? Any questions for each other? Jane?

DR. BALLANTYNE: I'd like to ask Susan whether you have any findings from your thousand patients over -- I've forgotten how many years you said. But you must have considerable amount of evidence.

DR. SUSAN HORN: We're only beginning to do the analysis because we had to merge quite a bit of start data in order to get to the point where we are right now. We had longitudinal data of certain types for many years along the way for the patients who are coming back to these places that routine care is being chronic pain. But we only started asking the patients as part of standard of care for them to answer about their pain. So we can follow that for a shorter period of time. It's now about a year and a half or so, in that period of time.

So we were waiting to accumulate that better data because, as I think you indicated and several other speakers did, that if you just ask providers about what they think the level of pain is for a patient and try to use that as well as the functional characteristics of the patient for the data, it's often even hard to find how they've described that in their records in standardized way.

Now we've got all that standardized in this database, so we're just accumulating and beginning to look at these questions at present. But this is the time. The threshold is really -- we've gone over that threshold, we think, in terms of having enough data to really start addressing many of the issues that you have so rightly described today and are going to be so important to see what we can get in terms of answers.

It will give much in the future, however.

DR. DWORKIN: Mac first and then Mike.

DR. GALLAGHER: Susan, I wanted to follow up that question. Is your sample a consecutive

sample, complete sample? In other words, all the patients coming in to a clinic?

DR. SUSAN HORN: That's right. Of course, if a patient says, "I won't answer the questionnaire," what we do is the clinician will then ask those same questions of the patient. This has actually been the way that we've made sure that we get almost complete data.

But it is everybody. And that's because, again, it's been standard of care. They decided not to have it be -- since it really wasn't any danger, we didn't think that -- the IRB did not think that this was a problem in terms of just collecting these data and then being able to analyze them. So they considered it standard of care to ask the patients and then to be able to get the other data that the clinicians are recording.

DR. GALLAGHER: And follow-up to that, are the patients in a primary care or pain clinic setting? What kind of a context?

DR. SUSAN HORN: The present group of patients are in pain clinic settings, both at

Sloane-Kettering, which is mostly cancer pain and survivors of cancer, and then non-cancer pain in two other settings, at Cornell and at Hospital for Special Surgery.

But one of our plans is to expand this database out into primary care settings, at least starting in the New York area and in other areas across the country, because Dr. Inturrisi, who has worked in this field for years, has a lot of connections. And we have to expand into all of those areas, we think, for the future.

DR. GALLAGHER: That's exciting because the Department of Defense is working with the Promise NIH group to develop a similar kind of a data registry for consecutive sampling of all patients coming in with a complaint of pain. So I think the field is going to be taking off.

I know Sean Mackey is also working at a similar project at Stanford. So I think this is going to give us the databases we need for answering those kinds of questions.

DR. DWORKIN: Mike.

DR. ROWBOTHAM: So I have a comment/question for Frank Porreca. One thing in all the preclinical packages for any new compounds being developed is that there's always studies in animal models where they compare the experimental compound with opioids.

One thing that you mentioned, and another thing that's in the literature, more the headache literature, one is this belief that if a patient is on an opioid, that they're no longer able to respond to non-opioids. That's all over headache literature.

The other is you mentioned that if you had an animal on an opioid and you had an effective therapy, that the animal would discontinue using the opioid. Do you think that's a viable model to include in preclinical packages?

DR. PORRECA: I'm not sure how to address your first question regarding whether or not there would be a response if there had been pre-exposure to an opioid, and particularly with the extended duration of therapy, because in animals, there's

substantial evidence that opiates can produce adaptive changes on their own. That might be considered pro-nociceptive.

Now, whether that actually happens in humans, it might happen, but it's not really clear which humans it may actually happen in. So how big a clinical problem or an issue that is, I really don't know. So this concept of opiate-induced hyperalgesia may be true, and it could limit the response that is seen with another mechanistic therapy.

Now, the second question, though, I can speak to perhaps a little bit better, and that is that in preclinical settings, one of the things that we've emphasized is trying to understand the motivation on the part of animals to seek relief from ongoing pain. And that seems to capture something that I think is quite translational because humans, too, have strong motivation to seek relief from ongoing pain. So we are not as much interested in the actual mechanism, the molecular mechanism of the molecule, as much as whether or

not it changes that motivation.

So Jeff Martin and Jim Eisenach at Wake Forest University did a very, very nice study where intrathecal administration of clonidine, an alpha-2 adrenergic agonist, was administered along with a paradigm in which opiates could be self-administered by animals.

What was very clear is that if you provided some pain relief, that animals would self-administer opioids less. So they would take less opiate. They would take it less frequently. And they would work only for the pain relief.

So that was the key that I think is evident, that if you have multiple mechanisms of action, that, in fact, this could provide synergy. And one of the things that's not often considered -- we talk about the actions of opiates at cells and at receptors. But opiates really, again, work in circuits, and they work through engaging multiple sites of activity in the brain, in the spinal cord, activating descending inhibitory pathways and releasing norepinephrine, for example, that

connected alpha-2 adrenergic receptors to synergize.

All of that changes the potency of the opiate -- the dose ranges at which the opiates could be effective, and probably provide the separation from side effects that allow them to be used clinically.

So I'm trying to say the answer is yes, that I think that in the preclinical setting, that looking at opiate-sparing actions is very valid, and I think it's something that hasn't been done enough and maybe should be emphasized even more.

DR. DWORKIN: Mark?

DR. HOCHBERG: So maybe start with the direction to Dr. Raja, and then others might pick up afterwards.

So in terms of the data on efficacy of opioid therapy in chronic non-cancer pain, we know there are other agents that were also mentioned this morning that have efficacy, some of the tricyclics, the SNRIs, gabapentin, pregabalin, et cetera.

I guess you mentioned your study, which was I guess the three-arm crossover study, where one of the arms had a tricyclic antidepressant in it. But in the world of systematic reviews and meta-analysis, which Dr. Turk may have criticized a little, there's this technique of indirect adjusted comparisons, and the newer technique of network meta-analyses.

I wonder if anybody has applied that to compare opioids to these other classes of centrally-acting analgesic agents for chronic non-cancer pain.

DR. RAJA: The answer to the last part of your question, I'm not aware of any network meta-analysis that's been done comparing across drugs such as tricyclic antidepressants and opioids.

Part of the analysis that we did within our own study, where we had patients on both classes of drugs, that is a crossover design, one of the things that we thought initially, partially, is that there would be some relationship between the

response to the tricyclic antidepressants and the opioids.

So we did kind of a correlation plot, and lo and behold, there was an absolute lack of correlation between the response to one class of drug and the other class drugs, suggesting -- and they were a small subset of patients who responded to both drugs. There were many who responded just to opioids, and the others would just respond to tricyclic antidepressants.

But in this kind of efficacy trial, we don't know whether this lack of correlation is because of lack of efficacy or because of individual variability in their side effects or tolerance of those drugs.

So the only thing we can say is there are clearly subgroups of patients who do not show an efficacy to an agent such as a tricyclic antidepressants and yet have a dramatic response to the opioids, and vice versa as well.

So that's where we feel that the choice of drugs are important in the sense that patients may

have either adverse effects that limit the ability of a physician to titrate the drug, or a lack of efficacy because of mechanistic or a number of other factors.

DR. DWORKIN: The last question from Dennis. Dr. Turk. Well, actually, I'm going to have the last question.

DR. TURK: This is for Raj, and it's building off of, I guess, Mark Hochberg's -- not his question but his presentation.

In your reviewing the literature -- and you did a lovely job in the limited time to do that, but we tend to hear, and these guidelines tell me, that opioids work. And often, in my reading of that, that appears to be based on statistical significance.

As you look at the literature, did you have an opportunity to think about what minimally important difference, a substantial benefit, or what the patients are saying about how satisfied they are with the treatment as well as what we're hearing from the statistics?

DR. RAJA: The data suggests that across studies, the effects of opioids is a reduction of somewhere between 1.5 to 2 on a zero to 10 scale. And when compared to the response to placebo, the difference is somewhere between .5 to 1, or less than 1. The studies by Farrar and others have shown that a 2-point difference is a significant difference, according to the patient's response.

So overall, the average change in pain from baseline to the end of the study is somewhere around 1.5 to 1.9 in the zero to 10 scale. And the majority of patients would say an approximately 2-point change is significant.

DR. TURK: Can I follow up?

DR. DWORKIN: Sure.

DR. TURK: So that's marginal. And when I reviewed the literature, the overall pain reduction is about -- that weighted average by sample size is about 35 percent pain reduction. And given the Farrar data, at least it doesn't look like the opioids are having that great an effect. They're marginal even when they get statistical significant

differences on pain reduction. But the patients aren't saying -- it doesn't sound like they're saying that they're getting a huge benefit.

A 1- to 2-point change on a zero to 10 scale is 15 to 20 percent pain reduction. I don't know -- I'd be very interested in surveying the patients to know about that.

DR. RAJA: Sure I think I agree with you, it's not the Holy Grail for treatment of chronic pain. But there would be two factors involved. That is, the majority of these studies, when they are titration-based to maximum tolerable effect, one is looking at the balance between efficacy and adverse effects, which often is a limiting factor in the use of opioids.

Second, a lot of the analysis is based on an intent to treat, so we are looking at the overall effect in patients who dropped out because of the adverse effects as well as those patients who have continued to go on. So in some respects, we may be underestimating the benefits in those who may have had a benefit.

DR. DWORKIN: I want to ask the panel one question about the research agenda before we open it up to the audience. So if you're in the audience, start thinking about whether you want to go up to a microphone.

My research agenda question is the following. I'm a lumper rather than a splitter. And I heard three buckets, really, of research ideas this morning. One is a kind of bucket of -- Raj started it -- open label cohort study. Jane suggested such an effort could use electronic medical records. Susan talked about your effort in New York City.

So one bucket of research ideas seems to be this kind of open level cohort study with as large a sample as possible, looking at opioids alone and in combination with other treatments, pharmacological, non-pharmacological.

The second bucket I heard was some kind of randomized trial. There was some offline discussion about whether that should be a standard parallel group trial or a randomized withdrawal

trial. One could have withdrawal to placebo and maybe withdrawal to another drug that is efficacious and might be thought to be good at replacing an opioid.

So the second bucket is a kind of randomized, maybe blinded, maybe not, maybe active placebo, maybe inert placebo, type of trial.

Then the third bucket I heard, and it was Pam's interesting idea, about whether, given what we now know and, I guess, existing labeling, could intensive educational efforts with perhaps primary care providers really have an important, perhaps dramatic impact on outcomes?

So in terms of how to spend -- let me assure you, it's not my $15 million, it's somebody else's $15 million. So with respect to how to spend $15 million, those three buckets, do they capture all the ideas that you all have had about a top priority research study, or is there something that doesn't fit into one of those buckets? Dr. Turk?

DR. TURK: The trouble with the buckets is that it really has to say what's the question that

you're particularly interested in? If you're the FDA and they want to know about the drug efficacy, they may be happy to think you should educate physicians and do a better job, but they may not view that as their priority.

So I think the research question you have may decide how you'd allocate your $15 million among the buckets.

DR. DWORKIN: I guess what I was thinking -- and I should have stated it; you're absolutely right -- is a top priority research study that would really inform our knowledge off intermediate to long-term efficacy/effectiveness of opioid analgesics.

Any other design? David?

DR. SIMPSON: Well, before we put something into one of those study buckets, I think what we need to do is back up for one step and ask whether we have the right measures to assess efficacy risk, both to the patient and to the society.

So, for example, yesterday in the Q&A open session, we've heard people using the same general

bucket of information and coming at this issue with vastly different recommendations and perspectives on what to do. I would argue this goes beyond science into philosophy, religion, and the like.

So my plea would be, can we develop measures, hopefully validated, that will combine issues of efficacy -- does it work -- with the risk to the patient -- is, adverse effects. And then the third, even more challenging issue is risk to society. And can we combine that into an analyzable, statistically appropriate fashion that we can have some informed data-driven answers?

DR. DWORKIN: I take Dennis's point that we need a clearcut hypothesis for the $15 million study, and certainly your point, that we need valid and appropriate outcome measures and methods of statistical analysis.

But given that no one has raised their hand saying that there's a research design that's in a different bucket, Mark?

DR. HOCHBERG: No. I guess I would not say it's a different bucket, but I would cite potential

examples of what you put in your buckets. But I'll hold off on that.

**Questions and Answers**

DR. DWORKIN: I think we all would love to do that, actually. But I think I want to give time for comments from the audience. We have 15 minutes left. If you'd like to ask a question or make a brief comment, remember, the ground rules are one question, no follow-ups, because we only have 15 minutes, and the microphones are already filling up.

Sir?

DR. ZACHAROFF: Great. Thanks. Kevin Zacharoff. And Charles stole my question earlier, so I don't have to ask it. Dr. Simpson definitely touched upon it, but I haven't heard the panel give some feedback on it, and I agree with it wholeheartedly.

How willing -- and whoever wants to answer this question. How willing would the panel be to take the word "cancer" and "non-cancer" away from being in front of the word "pain"?

That's my question.

DR. DWORKIN: You know what? In the interests of time, I'm going to answer your question. I think we could probably all agree in this room, and you can talk to me during lunch if you don't agree with what I'm about to assert, that there is non-cancer pain in a patient with osteoarthritis or postherpetic neuralgia; that there's cancer pain in a patient with active, if you will, metastatic disease.

Then there are these patients who 15 years ago got a taxane and now have chemotherapy-induced peripheral neuropathy, or 10 years ago had a mastectomy and now have chronic post-mastectomy pain syndrome; and that depending on how you write your inclusion/exclusion criteria, those are either cancer patients or non-cancer patients.

I personally don't think it gets us very far, given that we only have 10 minutes left before lunch, to have a discussion about whether that group of chemotherapy neuropathy patients, post-mastectomy patients, et cetera, et cetera, are

cancer or not.

I think we can all trust that the FDA, host of this meeting, think that that's a very important question, and that when the time comes, they'll think through the answer. So that's my answer. And so one question, one answer.

(Laughter.)

DR. DWORKIN: Jas?

DR. SINGH: Jasvinder Singh, University of Alabama at Birmingham.

I want to follow up on Dr. Simpson's suggestion with regards to combining efficacy/effectiveness and adverse events/harms into something that might look like a single statistic.

One of the issues that we've discussed, I guess, one of the ways to go there, is actually -- I mean, it's a long process. But there is a matrix being developed by one of the measurement groups that I work with which tries to, in a very simplistic way, trichotomize harms and trichotomize efficacy based on an a priori consensus as to what's small change, moderate

change, humongous change; small harm, moderate harm, humongous harm.

Then he can actually go to individual level RCT data and try to put patients from RCTs in those. And he can do the same thing as observational studies.

What's required prior to that is actually a consensus as to what's small, medium, and humongous in each of those categories. Again, it's a simplistic approach, but does actually take into account some of the pluses and minuses, and may be one way to look at it. Obviously, FDA has thought about this for a long time and may have better solutions. But it's the 3 by 3 sort of matrix that's being tested in one of the RA treatment trials that we are looking at that right now.

DR. DWORKIN: Thanks, Jas.

Sir?

DR. THOMAS: Yes. Hi. Dave Thomas. I'm with the National Institute on Drug Abuse and a member of the Pain Consortium. And I wanted to comment on the bucket comments or whatever,

discrimination.

Just one comment, we are doing a lot on pain education, and that's one of the buckets to cover. The problem with doing a big clinical trial on opiates as an approach is that -- one of the problems, at least -- you're going to get a very diverse population in terms of sex, in terms of ethnicity, history of drug abuse, their genetics. The very diverse population might -- opiates do work differently on different people. So at the end of that clinical trial, you might find that you had 10 percent success rate, and therefore you might get a .3 change on the visual analogue scale in terms of pain. It's a failure. But if you can help 10 percent of the people, that can help 10 million people if it's applied.

So our approach -- and that's what I want to comment on -- is to do like a hybrid, where you do a pain registry to find out what populations look like, what type of person, what type of delivery, and what circumstances and combinations of drug might work. And then use that to inform a more

focused clinical trial that has the advantages of all the controls.

DR. DWORKIN: I certainly don't disagree with that, and it sounds like you're suggesting NIDA might be interested in funding this effort.

(Laughter.)

DR. DWORKIN: So does anyone on the panel want to say anything beyond that we would really appreciate NIDA's support?

(Laughter.)

DR. TURK: My email address is turkdc@u.washington.edu, and I'll be happy to talk to you about it.

DR. HOCHBERG: And I think it's a great idea to look at data from observational cohorts to see what approaches are being used, and then to try and use those data to help design the study.

DR. DWORKIN: So we have two buckets now that have a bridge between them.

Sir?

MR. ALTARIFI: My name is Ahmad Altarifi, and I'm a graduate student at Virginia Commonwealth

University.

My question is, in all respects to all clinical trials, where there is a lot of funding going to the preclinical, the target of a preclinical is either to find new analgesics or try to find or understand the mechanism for advantages and disadvantages of using opioids. Now, preclinical studies have been for a long time ago, and they have good and promising discoveries about new analgesics.

My question exactly to Dr. Porreca as a basic scientist, most of the discoveries in the preclinical failed in the clinical trials for new analgesics. Why do you think there is this disparity and the association between the preclinical and the clinical fields and analgesic field? Thank you.

DR. PORRECA: Well, that question is quite complex. And I actually was a participant in the NIH Blueprint Pain Consortium Symposium that was held before this, and I gave a lecture on that very topic. But I'll just make the following comments.

The main problem is that we really don't know if our preclinical hypotheses are effectively ultimately tested in the clinical setting, in large part because we don't really know what underlies pain in individual patients. That's the first problem.

The second problem is that we assume that the molecules that we actually take into clinical trials are excellent molecules, and they may or may not be. And so in the end, if a clinical trial actually fails, it is not completely clear that the underlying preclinical hypothesis was incorrect, or that the patient group was wrong, or that the molecule itself was insufficiently able to reach and engage the target, was limited by unpredicted side effects, et cetera.

So a very complicated question. Very well worth thinking about. And certainly lots of things we can do better. But not a short, easy answer that I can give you to that.

DR. DWORKIN: Clifford?

DR. WOOLF: It seems to me there's a major

tension between the gold standard for evidence, randomized, controlled trials -- and Dennis Turk gave a very good summary of the problems that RCTs entail. I'm a bit worried, though, in the enthusiasm to go for observational studies, that we do not confuse the fact that they can generate data but not evidence.

We've seen that with GWES (ph), that at best they may show us associations between treatment and response, and the response that will be recorded will be critically dependent on whatever questions happen to be chosen, even if they're standardized in the patient cohorts; and that in the end, if we're going to actually move from associations to actually saying treatment A causes outcome B, we will still require scientific approaches that deal with causality rather than associations.

DR. DWORKIN: Yes. So Susan, could you comment on Clifford's question? In other words, all the potential known and unknown confounders in your data that really make it very difficult or perhaps impossible to draw causal inferences.

DR. SUSAN HORN: This idea that causality is either there or not there, I think, is something we have been taught in the beginning, but I really have questioned it over time in the following sense.

Yes, a randomized trial is supposed to give us causality, and observational studies are concerning to many people because they don't know if they're missing confounders that people have not measured.

But I think that there really is a spectrum here and that we can get closer and closer to observational studies telling us good information about what might be causing things if we have enough accurate and comprehensive confounders that we can then test our assumptions on, and if we have a big enough sample to be able to have enough observations to ask these questions.

That's what we have been trying to do over time, which is why, in the studies that I've been mentioning to you, the practice-based evidence studies that were the design used to put together

this chronic pain registry, you get both the providers as well as the patients to tell you things that they feel are making a difference or that they have known from their previous work and experience.

So you don't limit the kinds of variables that you collect. You really collect everything that somebody suggests, and then you see to what extent it makes a difference.

Now, is it the absolute only answer we need? No. I totally agree with Dr. Woolf that we're going to need a variety of ways to be able to look at these questions. But as of today, to try to think of additional ways that we can move this field forward that will be more applicable to begin to address the various issues that we've all been talking about the last two days is to be able to collect more detailed, comprehensive data from the actual practice of care because that's really where the rubber hits the road.

We're really talking here about effectiveness, what works for the patient sitting

in front of you there that you're going to be treating. The patients want to know this, too.

I think we can get a lot closer to that today because we have the ability to collect large amounts of data on people. The patients are now participating. And we've got computers that can analyze many, many variables, which we couldn't do in years past when we didn't have computers to help us handle this.

So I think we're in a new era to begin to look at alternative designs that can help address many of the questions that have been raised, as I say, in the last two days in important issues.

DR. DWORKIN: David has a quick comment, and then we'll take the two questions at the mic, and then we're going to have lunch.

DR. SIMPSON: Well, just to echo Clifford's concern, there does seem to be a worldwide move, certainly in Europe and now moving into the States, of moving away from placebo-controlled trials, whether it be for ethical reasons, for pharmacoeconomic reasons using active comparators,

and the like. And I think we do need to be cautious about the strength of conclusions and the strength of the evidence that we can draw from these types of both non-placebo trials and observational studies.

We're talking about investing an awful lot of money, and I would put a strong word into putting that money into the places where we can extract the best and the most powerful evidence.

DR. DWORKIN: sir?

DR. SILVER: Hi. My name's Harris Silver. I was up here before. I'm a drug policy analyst. I'm a physician. I'm mostly an epidemiologist, and I am just really following up now on what was just discussed.

I think addiction is a huge confounder in these studies. It is extremely hard to manage. I have great concern about it every time I read a study, including a very well-controlled, randomized, controlled trial. I think it's very hard to determine if tolerance is about losing pain control or about losing euphoria.

Addictionologists can spend hours and hours trying to determine if a chronic pain patient is truly addicted. And I was wondering if anybody had any ideas, and if anybody had as deep a concern as I do about measuring the efficacy about how to better manage the internal validity of the study around addiction.

Like, for example, you could end up having a lower effect because people may want more drug, and will tell you they're in more pain than they really are because of their addiction. So you could end up having -- you may actually have a drug that's more efficacious.

So if anybody could address that. I know it's complicated.

DR. DWORKIN: Jane, do you want to quickly comment on it?

DR. BALLANTYNE: Well, I know we don't have much time. But I wanted to comment on Clifford's question just briefly. You know, it's really interesting when you read the history of what happened with tobacco. And there was huge

resistance to believe the epidemiological evidence because, you know, the same old issue, that we can't prove causality.

In fact Dole, who finally wrote the seminal study, writes very eloquently about what elements you need in epidemiological data where you finally say, we have to believe this. And what Susan was saying is we have new technology now. We have new means of getting at far more patients with far more data. So I think we have to start thinking about this and stop thinking about, you know, we're going to get everything from randomized trials.

The question about addiction, I think that where -- addiction/dependence, so I think you have to say every patient gets some sort of dependence, whatever degree it is, is really the key thing. Because when you're dependent, that affects your pain responses.

So that makes designing the trials really difficult because your dose effect is not really a dose effect at all; it's dosing history effect. It's whether you're in the process of going up on

your dose or whether you're tapering, whether you're seeing withdrawal, which pain is a very strong symptom of withdrawal.

So dosing history is really a confounding factor when you're trying to design these studies.

DR. DWORKIN: Last question, sir.

MR. SRIVASTAVA: Hi. Sri Srivastava from Astex Therapeutics (ph). My question is that most of the randomized clinical trials in pain have shown very high placebo effect.

The comment I would like to hear, that whether we should be even using this non-placebo designed trial; and if not, what should be the appropriate kind of control? Not the active comparator, but besides that, if there is anything that can be used for that.

DR. DWORKIN: How about Mike? Do you want to tackle that?

DR. ROWBOTHAM: If I heard you correctly, the question is whether or not placebo should be included as comparators. The way the medications are regulated is that you just have to -- if

there's no gold standard for that particular class of molecule, then you can compare it against placebo.

I think if you're trying to do a very large trial, something that can be done in a primary care setting, it's much more complicated to try and do a placebo-controlled trial. It has more risk to it in the patient's eyes.

So looking at randomizing across different accepted, approved therapies for a given type of pain allows you to compare those therapies head to head without worrying about whether or not any of them are actually effective compared to something like placebo.

So it's a simpler type of study to do, and still allows you to ask the question of what is the best among a variety of different approaches, and what are the harms associated with each of those approaches.

DR. DWORKIN: Last word from Dr. Hochberg.

DR. HOCHBERG: I would think in this large, let's call it pragmatic, trial, that you would

compare agents which have already been shown to be efficacious compared with placebo, and compare them to each other in a structured fashion, whereby individuals who didn't have an adequate response after a certain period of time, as you suggested and as has been done on other studies, would move on in a certain protocol to either go crossing over into a different arm or would go onto a different type of therapy.

DR. TURK: So the model is very much similar to what was done in the newly-diagnosed epilepsy study that I showed a slide about, and that study has been going on for more than a decade.

DR. DWORKIN: Okay. I'm going to have the last word. I'd like to thank all the speakers for their wonderful presentations, the panelists for your great discussions, and then all of you for a terrific set of questions. We will resume here after lunch at 1:30. Thank you all.

(Applause.)

(Whereupon, at 12:34 p.m., a luncheon recess was taken.)

A F T E R N O O N  S E S S I O N

(1:36 p.m.)

**Panel 4 - Douglas Throckmorton - Moderator**

DR. THROCKMORTON: If I could seek folks to start sitting down, we'll get started on this last session for the afternoon.

The people that you're going to be hearing, the next three speakers, are going to be individuals with experience in using the drugs that we're talking about here, either from a physician's perspective or from a patient advocacy perspective.

We're lucky to have Penney Cowan as the first person that's going to be talking to us. She's the chief executive officer of the American Chronic Pain Association.

I met Penney working on the opioid REMS issues now a couple of years ago, and she continues to send me information, continues to help me understand the opioids from the perspective of the individual working with chronic pain.

Penney, I look forward to your presentation. Thank you very much.

**Presentation – Penney Cowan**

MS. COWAN: I'm going to be talking to you from a different perspective than we've heard today. As soon as we get the slide up, I will start telling my story.

I'm a person with pain, and 32 years ago I started an organization called the American Chronic Pain Association to let people know that it's actually possible to live a full life with pain. And so over the last 32 years, we have talked a lot about people with pain. And really, from a different perspective, what is chronic pain? We've heard a lot of people asking that question today.

From my point of view, chronic pain is what turns the sufferer from a person into a patient. And the most important thing that we need to do is to change that and help that patient, the passive patient, turn into an active participant in their health care. That's really important.

No matter what, no matter how bad the pain is, we're willing to do absolutely anything to get relief. That's one of the problems. We are so

desperate. And a lot of times when I talk to people, they'll say, if it was just the pain, if I could just get rid of the pain. And the pain really isn't the major factor. It's the fear of the pain. That's what's really controlling us. And that's what's controlling so many of them when they may not take their medications as prescribed, because they're afraid, okay, if one works good, maybe two will work better, or if I'm going to be going somewhere. And that is part of the problem. It's the fear of the pain, never knowing.

I know I've heard people talk about, well, it's 24/7 and they have pain all the time. But really, your pain, it comes and it goes. You have good days and you have bad days. It's not all the time. But the control of the pain, the fear of the pain, that is 24/7, and that's part of the problem.

Our expectation is -- I mean, look what medicine can do today. You can give us all of these medical miracles, and yet it doesn't make sense why you can't take away our pain.

So we get stuck in that little maze there,

and we go from one thing to the next, never finding our way out. It is just this jungle that we're trying to get through.

So what we really need is a balanced approach. And I've heard a little bit about it today. I've heard people talk about the other modalities to pain management. What we really haven't heard too much about is the responsibility of the person with pain, and that's really where I'm going to come from today, because a lot of what we're hearing is about the opioids, which really unbalance the treatment. That's not the only piece that we need to actually live a life of pain.

To go from that mindset of the disabled patient back to functional person, we need more than that. And we look to our health care providers to help us do that. The problem is, they're not trained to do it.

A couple days ago, in the NIH meetings that we had, I heard someone talk about there were seven hours -- I always said two hours of pain medicine -- seven hours is all a health care

provider gets in all of that training. They don't know how. The only thing they really know how to do is prescribe, and that's what we expect of them; nor do they have the time to help people.

So what do we always hear?

(Screaming sound played.)

MS. COWAN: Learn to live with it, and now you all know what we feel. We just want to scream because we don't know how to do it. And for six years, before I was able to go to a pain management program -- and that was 33 years ago -- that's what I kept hearing. Everybody told me, just learn to live with it. The problem is, that's where it stopped. No one ever told me how to do it.

The longer our pain goes on, the further down we go on this road, and we disappear. Who we are disappears, and we become our pain. I don't know how many people I heard yesterday, and I still hear them, refer to themselves as chronic pain patients. They have to be a person with pain because if your pain defines you, then you're never going to move past that. We need to not allow

ourselves to disappear down that road.

When you tell someone to learn to live with it, that's what it looks like. I have no idea what that is. All I know is, if you asked me to solve that, I would be here the rest of my life. I'd never be able to get home and see my grandkids. I would be trying to figure that out.

However, if somebody taught me how to solve this, if I really paid attention and worked hard, I bet I could solve that problem. And that's exactly what it's like when you tell someone to learn to live with pain. You can't just say, "Solve it." You have to show them how.

So part of what our organization has tried to do over the years is to change that very complex formula into something simple, one plus one equals two. Everyone understands that. And I don't care how smart they are; when they're hurting, it's hard to think. It's hard to concentrate. One plus one is easy to do.

But the most important factor is that the person with pain has got to take an active role.

They cannot be the passive patient. They really need to get involved and be part of the treatment team. And so that's what we talk about.

What is the goal of pain management? It's to improve the quality of your life, increase your function, and reduce your sense of suffering. Nowhere in that goal do we talk about getting rid of the pain 100 percent because that may never be possible. But if we could achieve those three things, it would be pretty good. Very good.

We have a couple communication tools because if we're going to be part of the treatment team, we need to be able to communicate with our health care provider in that very short amount of time that we have so that they get the messages that we need to hear without us looking like chronic complainers and everything else.

So we have this thing called -- and I always hated the scale on zero to 10 for pain. So instead of -- and remember, one of the goals of pain management is to increase your function. So this scale, instead of measuring your pain, is going to

measure your function.

So if someone says they're at a zero, you know exactly what that means. They can't even get out of bed, all the way up to a 10, where they can get up and do normal, everyday activities.

We also have something called a pain log, and this is actually also interactive on our web page. And it's going to measure their pain, and it's going to measure their stress, their exercise activity, their sleep, the fear of the pain, taking medications as prescribed, their side effects -- constipation, sexual activity -- their appetite, mood, how isolated they become, how much alcohol they drink, and how worried they are about finances.

All they have to do is circle where they are on that. Can you imagine how much information at a glance a health care professional can get when they come into the office and say, "How are you doing," and you show this?

More importantly, what it does is they begin to look at that pain score and they can then begin

to connect it with the other things that have a major factor on how well they're doing and how much they're suffering. And it may be because they're not taking medications as prescribed, or they're really having issues with constipation so they stop their medication altogether.

This is now actually interactive on our web page. It's all free. Everything on our web page is free. And so they can go in and do this on a day-to-day basis and actually print out graphs and bring to you.

Medication. We've been talking about opioids, and there's a real problem. But my belief is it's not just about the person with pain and the health care providers. It goes way past that. And I think we need to reach out way beyond just people with pain and health care providers.

So we designed a public service announcement -- it's a 30-second spot -- and the only way I could figure out to get it in front of people was to put it in movie theaters. So we got funding just to put it in one in Kentucky last

year, and we played it for an entire month. It's actually PG-rated; we had to go through the rating system. So I'm going to show it to you right now.

It's not going to play? That's too bad. You can fix it quick? If not, I'm going to go on. No? Okay. Just go on. That's too bad.

It talked about that there are now 15,000 deaths in the U.S., and you shouldn't share. You should dispose of it properly, store it appropriately. But it's got pictures, family pictures, and each time it goes past a picture, somebody in the picture just disappears. So it's really quite powerful.

So, really, what I want to talk about is what is the responsibility of the person with pain? In addition to taking their medication, whatever that might be, what do they need to do? And I think accepting the pain is really one of the first steps.

They have to realize that there may always be some level of pain their life, but that doesn't mean that it's the end of life, that you can still

have a life. Educate yourself. Understand that. Work with your health care provider, and then take an active role. We can no longer be passive patients.

Again, all we've been talking about for the last day and a half is about opioids, but there's so much more to it than that. That's only one of the many pieces. And the person with pain can get actively involved.

So one of the things we talk about is their priorities. And a problem with pain is that you tend to let things go. When you don't feel well, you just let them go, and they sort of pile up. And you have this huge mountain of things that you just can't get to. And it's overwhelming. So what do you do? Rather than taking on the mountain, you just do nothing at all. So it continues to grow, staying in that passive role.

So what is really important is for people to begin to identify what's important to them right now, to give them a reason to get out of bed in the morning because if you're hurting that much, why

get out of bed and continue to hurt?

So we help people to identify their priorities. What's the most important thing right now? And we ask them to just get a whole bunch of 3 x 5 notecards and write down everything that they think is in their mountain, all the stuff that they thought they should do, didn't do, break them down, one on each card.

When they think they've got them all written down, then just lay them all out in front of them and ask themselves, looking at all those cards, what's the most important thing to you right now? And pick up that card, and they have their number one priority. And at least they have a starting point, somewhere where they can start, because pain is so overwhelming, it's hard to figure out where to start.

Once they have their priority, they really need to set realistic goals for themselves. But too often we set ourselves up for failure. One of the problems with pain -- and I said it goes up and down -- on those good days we have so much guilt

and there's so many things that we know we should do, that on a good day we try to do it all. And you know what happens. The next day you can't move. And so what do you tell yourself? I can't do that. I'll never do that again. And that's where the elimination of all the activities come from.

What if you narrowed some small little thing down and took one tiny step? And then maybe listened to your body. And we don't do that either. We push because we feel guilty. And when we feel that first ouch, we go, I can do a little more. And so we push a little more. And then the second ouch, and we push a little more. And we really don't stop until it screams at us.

We should begin to listen to our body. That's part of our responsibility. No one else can do that. And then as we narrow these goals down, what's going to happen, you're actually going to see that you can accomplish something. Pain takes away not only your identity but your self-esteem, your ability to do everything. So we need to begin

to build that back up again.

Your basic rights. And this is where I like to tell new groups to start. We have support groups all over the country. On the basic rights, we need to empower the person. If they're really going to take an active role, we need to empower them.

Here are the basic rights that we talk about, things like the right to be treated with dignity and respect. And you have the right to ask why, and you have the right to say no and not feel guilty. But more importantly, one of the ones, and my favorite right, is that you have the right to make mistakes.

You also have the right to do less than humanly possible, and that one is really key to people with pain. So on a bad day, you have the right to do less -- I mean, on a good day, you have the right to do less than humanly possible. Enjoy it. Don't push yourself beyond limits.

You have the right to ask for help. You have the right to change your mind. These are all

very important, basic rights that allow people to be empowered. And it is amazing. When you start teaching these to people in our groups, they just begin to feel like, okay, maybe I do have some rights. Again, pain takes all that away.

Recognizing your emotions. And I like to use this picture, and I always talk about the guy is the one -- the man is the one who has the pain. And we think that it's only affecting us. But that's his wife sitting behind him. She doesn't look real happy because it's not just about us. It's about the whole family unit.

Emotions -- and they all say, oh, you're just depressed; that's why you're in pain. We all unfortunately have heard that at one time or another in our journey. But of course we are depressed. Who wouldn't be? Imagine if you had the flu for an entire year, would you be happy camper? No, you would be depressed. So let's just say, okay.

But the problem is we tend to ignore our feelings. There was a book that I was given when I

went to the clinic, and I went there, actually -- I went to the Cleveland Clinic, to the pain program, and I went there to fail. I didn't believe any of this, by the way. And I was sure that nothing could help me; at that point in time, there was nothing that could help me. I couldn't even hold a cup of coffee when I went to the clinic.

The first thing they did was gave me a book to read. The book was called, "The Angry Book." And I thought, why are you giving me this? I'm not an angry person. And they said, "You have to read the book." And it's a very small book. It's actually still in print today. It's by Dr. Theodore Rubin. It's called, "The Angry Book."

So I read the book because they told me I had to do it, and I always did everything I was told. And in each chapter I saw another piece of myself. It described all these different kinds of anger.

What was interesting is I don't remember what those are, but what I remember is the takeaway message in the book was he talked about a slush

fund. And every time we ignore one of our feelings, negative feelings -- I'm a keeper of them; I like to stuff them away; nice people don't get mad -- and every time we ignore one, it stays with us. And so it builds up.

So I like to think about the slush fund as a bucket. It's a bucket. And every time we ignore one of our negative feelings, it's another drop of water in our bucket.

Now, imagine, it gets a little heavier and a little heavier. And what happens after it's full, and that one last drop? It's going to explode. It's going to go all over the place. And that's what happens with our anger and our emotions. We usually dump it on someone who we trust, a safe person.

But imagine how hard it is to carry a bucket of water around with you all the time. Our feelings, even though we ignore them and we think we're burying them inside, they're part of us, which is going to create a lot of stress. And stress is going to increase pain.

There are no wrong feelings, only inappropriate actions. We can't control our feelings. I mean, it's okay to feel negative about somebody. You may think you want to hit them, but you don't have to hit them. But you can feel like that.

Learn to relax. That's all you have to do. Right? Just relax. I went through biofeedback when I was there, and I had four sessions, and it was terrible because I tried so hard that instead of turning the sound down, it went up. It was terrible.

But it was nice because they made me tapes and said, "Take them home and practice them." And I did, and I really practiced them, and I practiced them. And it actually is now just a part of me. And it really takes a lot of practice.

If we could just go to this beautiful little island and lay on that warm sand, and you pick up the sand, and you know how it feels like silk running through your fingers, and you can hear the ocean crashing against the shores. If we could

just be there, it would be really easy to relax.

The problem is, that's not going to happen. So what I want you to all do for me right now, in your mind, I want you to count from 1 to 25, and at exactly the same time, say your alphabet. Can't do it, can you? You know why? Because you have a one-track mind.

So while you're thinking about being on this beautiful island, hearing those seagulls overhead and the palms swaying in the wind, for that second that you're thinking that, you're not thinking about how much your pain hurts. And so for that second, you've accomplished one of the goals, and that's to reduce your sense of suffering. It's a learned skill. It takes a lot of time. But it certainly is worth the effort.

I'm running through all this. I can give this talk in like two or three hours, so I'm really rushing through all this.

Exercise is another thing. People say you need to exercise. And again, many people with pain tend to be over-achievers. And so you want to

exercise. In our workbook, we have 10 illustrated exercises, stretching, and we have 18 exercises, the stretching exercises. And we have them in there so that people can go to their health care provider and get approval for them.

We can't make physical evaluations. We're not health care providers. And so we want them to take them to their health care provider and see which ones they're capable of doing. And once they get an approval, what we tell them to do -- remember, I talked about not setting yourself up for failure. And so maybe they approve three or four of them that you could do.

Well, we say, pick one. Maybe it's leg lifts. And before you get out of bed in the morning, just lift your leg as high as you can. That's it. And then the next morning, you do the same thing. And then the next week you do two, and maybe your leg is going a little higher.

Very slowly, you are going to build up -- first of all, you've gotten a routine now of exercise. And secondly, you now are beginning to

see that you do have ability and you can exercise. And very slowly, you will regain control and be able to strengthen those muscles because the more pain takes over us, the more deconditioned we become.

That was a big part of my problem. Every time I did something and they said -- you know, I'd tell the doctor what it was, and he said, "Then don't do it any more." And so it was to the point where I did nothing. And that was part of my problem.

Exercise is hard to do, but it's an important part of pain management. But you really need to look at the total picture, and so often what we hear people say is all the stuff they can't do, all the disabilities. And the way we as an organization like to think are about, what are your abilities?

We all know what pain does to us. We don't need to talk about our pain. What we need to know is, what are your goals? What are your priorities? What are your abilities? What can you still do,

and how can we build on that?

Quite often I will have a person say, "Pain is the best thing that ever happened to me because I really had to step back and look at my life and redefine it." I have a couple great videos on that but I can't show them to you right now.

Then the outreach, reaching out to others, and I think that's really what I've been trying to do for the last 32 years since I started the organization.

I'm going to end with our little red car. We use this little car as a way to illustrate a person with pain, except their car has four flat tires. We've been hearing for the last day and a half about opioids, and it may put air in one of their tires, but guess what? They still have three flat tires. They are not going anywhere.

So we have to ask ourselves, what else do we need to fill up those other three tires? And it's going to be different for every person. It just depends on what they need. They're going to have to work with a health care provider. They're going

to have to work with their family members.

Once they get all four tires filled, then it's their job to maintain that car on a day-to-day basis. You know, you don't take your car back to the dealer and say, "Wash my windshield," or, "Put gas in my car." That's our responsibility. If something goes wrong, we'll take it in for a checkup.

Thank you very much.

(Applause.)

DR. THROCKMORTON: Penney, thank you very much.

The next person is also someone that's been working in pain for a long time, working with the use of opiates for a long time, Fred Brason. Fred has a particular interest in overdose and overdose prevention, his Project Lazarus, something I've been familiar with, we've been able to draw on his expertise in the area of the use of naloxone. Very recently, he came and helped us with a public meeting that we held on the use of naloxone to treat overdoses of opioids.

He's going to be talking to us about the project and his own perspectives on the treatment of chronic pain.

Fred? Thank you very much.

**Presentation – Fred Brason**

MR. BRASON: Thank you. I'm very pleased to be here, and thank you again, FDA and NIH, for the facilities to have this opportunity, and for all of us to come together to learn more of this issue and what we can do regarding it.

I'm going to be sharing what we are doing in North Carolina and where that stemmed from with the experiences that we've had in approaching this from a community perspective, engaging all community sectors.

This is a list of the required disclosures. There's many more that I could put on there. The required ones are on there. I've put all of it on there because it's emphasizing that for a comprehensive approach, it takes a lot of comprehensive support. And we can't leave anybody out of the message that we're trying to bring and

the solutions to the community.

What we're doing in North Carolina with Project Lazarus is developing a community-wide, community sector engagement to educate, to engage, to be able to supply them with the materials, the resources, for each community sector to address the issue regarding prescription medications.

While at the same time, we're now collaborating with our state Medicaid case management system, who we're now initiating the Chronic Pain Initiative throughout the entire state, all 100 counties, all 14 Medicaid case management networks, in educating physicians, again, to look at reducing possibly the supply, the demand, the diversion, of course the harm, which, unfortunately, in North Carolina has been the overdoses.

I can also give you a massive list of others that are in this collaboration, from the North Carolina Medical Society, the North Carolina Medical Board, the North Carolina College of Emergency Physicians, the Family Practice Group,

the Dental Society, the Division of Public Health, the Division of Health and Human Services. We are all in one statewide collaborative to bring across the initiative to every community to address the opioid overdose and utilization.

Our model is based on public health and officials and research. I'll go through each one of these as quickly as I can. The professional community coalitions that we're building, that we're painting a picture and helping to develop in every county in North Carolina, and there is 100; and then what we're doing with the health care providers, the prescribers, the hospitals, the emergency departments, in every one of our communities in North Carolina.

Essentially, where we're starting is looking at the overdose deaths through the Office of the Chief Medical Examiner. Who died in North Carolina in each and every county from what is classified as an accidental poisoning? Somebody who did not intend to die.

It was not a suicide; but unfortunately,

because of the amount that they used or the amount that they mixed with it, whatever that might have been, it caused them to overdose and, unfortunately, die.

We're also looking at the data of the amount of hospital emergency department visits surrounding substance abuse, withdrawal, and overdoses, as well as the subsequent hospitalizations. We can also now track the prescribing patterns of every single county, all Schedules II, III, IV, and V, to look at those levels of every single county, and also how many prescribers are also signed onto the prescription monitoring program to check the history of their patients for every single county.

Then we do ongoing surveys. Initially, we just did one, that I'll share, with our local county health departments -- and we have 89 covering 100 counties -- and those health department directors to see what they knew as far as intervention and prevention of this in each individual county.

You can see here, North Carolina has been on

the same progression as the United States for overdoses. Epidemic level was achieved of 8 of 100,000 back in 2003/2004. In North Carolina, you can see 79 percent of the unintentional deaths are surrounding prescription medications, mainly opioids, 17 percent intentional, and then of course the rest undetermined, as unavailable for that.

In 2006, the cocaine, heroin, and methadone that had traditionally been the number one cause for the overdoses had the downward turn, and the synthetic opioids had the upward turn, and continues so far in that regard.

So we're very pleased that the cocaine and heroin and methadone is going down; unfortunately, I do have to say that heroin utilization in North Carolina seems to be on the upswing, as in many other parts of the United States, but thankfully, so far, it has not resounded in overdoses.

This from the survey from the county health directors, and as I said, we have 89 health departments. Seventy percent responded to this survey. And we asked them to do a survey of their

own community to determine what is going on, what is in place, what is happening regarding the intervention and prevention of overdoses, and the misuse and abuse of prescription medications.

You can see far and away that pill take-back days, number one, that's a hot topic. It's very tangible. It's very easy to do, and gets a lot of people involved, including law enforcement and the general public.

Then you can see it's kind of downhill from there, with the fixed disposal sites, the school-based, the medical education on chronic pain, the mandatory use of PMPs in hospital EDs, the ED case management that we were able to initiate, and how much is not being done in North Carolina. And unfortunately, because all of this is not being done, we are going to see an increase in the opioid overdoses in North Carolina.

Here you're looking at the percentage of North Carolina residents receiving an opioid prescription. On average, since 2008 through 2011, about 5.75 percent are receiving an opioid

prescription each month. In tracking this, you can see that it's been on a steady increase, though not declining in any regard other than little peaks and valleys.

But in looking at that, we can determine -- and now we're looking at which ones are extended-release, which ones are immediate-release; we'll have that information very shortly. But that kind of tells us, as what we've all been talking about, does, and is there the correlation between the upward swing of the prescribing and an upward swing in the overdoses. That is something that we can definitely look at and see a linear correlation with that.

But as we look at each individual county in North Carolina, the darker counties in this being the ones with the higher overdoses, the ones with the larger circle in orange having what we would consider the higher number of prescribing of the opioids in those counties, you can see that correlation.

But when you look at it at a higher level in

more investigative work, there are those communities that have high prescribing and low deaths, and then those communities that have what we would consider low prescribing and high deaths.

So it isn't something that we can definitively say is a cause, though in some respects we can show that there is a correlation. But in this, we've got to look at the communities as we do with the individual, personalizing the prescribing for that individual and what their condition is and what their whole modality is and the comorbid situations in their life, as well as looking at the same individual if they need treatment.

What is the personalized treatment that fits them to have the best success? We've got to look at our communities in the same light. What is the makeup? What is the influence? What is the environment? What is the society? What is the culture of that community, and address the intervention and prevention within that community according to that design.

That's what we've been doing in North Carolina because, as you can see with this bubble graph, the larger urban areas or the larger circles, there is less prescribing. And as you track the line upward, the more rural communities, the more economically depressed community -- your tier one communities, which we have 40 out of the 100 in North Carolina -- the prescribing levels have a tendency to go up with that.

So we have to look at all of those factors, not saying that the prescribing levels aren't warranted. I'm very careful, especially when I'm talking to prescribers, that I'm going on the premise that 100 percent of what you prescribed is for the right reason, the right purpose, and the right diagnosis. But neither the prescriber nor the pharmacist can control what happens to that prescription once it walks out the pharmacy door. That's where the community has to be engaged, according to what those issues are within that community.

So if we know that poverty is the driver,

then we have to understand poverty. We have to understand the lifestyle of those who are impoverished and the different dynamics of that, of situational and generational poverty. So that's some of all the dynamics we look into.

Unfortunately, I don't know why that slide is not showing up, but we'll move on.

Doctor-shopping. According to the PMP that we've had engaged since 2007, we're showing an average of individuals where 15 or 15 of your class II and class III schedule drugs have been on the decrease, as well as 10 or more, 10 prescribers, 10 pharmacies. The PMP is helping with that. There are peaks and valleys of that also.

But we don't just look at the PMP for data to police what individuals are doing, but also the public safety, the patient safety, of receiving one prescription from one doctor and maybe another prescription of something else from another doctor. And I can say in Wilkes County, North Carolina, 40 percent of our overdoses were also of an opioid and a benzodiazepine received from a variety of

sources. So those are some things that we have to look at.

But in looking at the physician education, health directors are telling us, and what we've been doing in the communities, didactic teaching isn't the method. It's lunch-and-learns, it's CMEs, it's academic detailing, it's grand rounds, and other modes in order to teach on chronic pain and all the modalities with that and prescribing.

So there isn't any one thing that we can target and say that's the way to do it, though in the rural communities we're finding the lunch-and-learns to be the more prominent and the more successful.

In looking at the PMP, the prescription monitoring program utilization, most physicians are now telling us through our surveys is they're looking at the behavior of the patient. They're looking at certain things that would be a clue, a flag, for them to address and look at that PMP, rather than just looking at it as overall, looking at the patient and saying, anybody I'm prescribing

an opioid to, that I should look at the prescription monitoring program; because they could very well be doing everything appropriately and everything correct, but they haven't told me that they're getting their benzo or something else from someone else.

So those are some of the things that we're working on with the North Carolina Hospital Association and the College of Emergency Physicians to help address that and promote that ongoing in the state.

Now, community awareness and the coalition-building, the school-based education, we're working with every age group so that they understand you don't take grandma's medicine. You don't take mom and dad's medicine. You don't go into the cabinet. If it's not prescribed for you, it could be against you. And so those are some of the things that we're working on culturally and educationally.

Of course, I'm doing community forums in every community in North Carolina, so I'm 70-some at this point, bringing stakeholders together,

coalition group, health departments, law enforcement, faith communities, the medical community, hospitals, everybody into the same room addressing the same issue without pointing fingers at either one, saying, you're at fault, you're at fault, and you're at fault, rather than saying, no; overall, we need to address the issue and address the problem, trying to make sure that we do not create an access to care issue among patients who have chronic pain who cannot get the care.

We want to make sure that that takes place, and if there is somebody who needs treatment, that we're able to get them into that treatment venue as quickly as possible through the referral mechanisms.

The supporting pain patients, I won't spend a lot of time here because Penney just did a marvelous job there. All of the things that she said, ditto here regarding chronic pain patients and helping them exist and function in their lives.

Of course, the pill take-back days, we know that they're going on. They are just an element of

a comprehensive approach. They are not a silver bullet. They're not going to fix the problem. But unfortunately, right now they are at the top of the list that everybody's doing. That's great, but there's a lot of other things that we need to be doing besides that. And so we're working on that in North Carolina and other areas.

The prescriber education, the patient and drug user risk reduction, effective drug treatment, ED policy on dispensing, we are doing that across the state. We have created a Chronic Pain Initiative toolkit for the primary care provider and the care managers who do the case management of the Medicaid patients who are chronic pain, that they will be under case management, some of those, because of the high levels of dosing and maybe high levels of ED visits. They're coming under a lock-in program of one primary care physician and one pharmacy so that we just kind of box things in a little bit without denying anybody care. It's a very extensive toolkit.

With the promotion that we've been doing in

Wilkes County, we have 70 percent of our prescribers using our prescription monitoring program while the state of North Carolina is at about 28 percent. So we're looking to double that within the next 18 months.

We've also created a toolkit for emergency departments because we found them to be fairly easy access for individuals looking for a prescription, looking for a pain reliever. What we did essentially, at Wilkes Regional, was developing a policy for chronic pain; individuals who are recurring to the emergency department no longer would receive a controlled substance, but something, an alternative, as well as a referral to where they can get their ongoing care besides the emergency department.

No more refills in the emergency department; mandated that the emergency room physician must check the PMP before prescribing. And no more 30-day prescriptions going out of the emergency department; 10 tablets, enough for three, four days so that that person can get to their primary care

physician, their dentist, whatever that situation may be. We do that by embedding a case manager in the emergency department to help those what I call frequent flyers get into the right venue of care.

In six months, we got a call from our hospitals saying, "Well, we got too many complaints and our visits are down." In nine months, the neighboring county hospital called and said, "What's going on? Your Wilkes residents are showing up in our emergency room." They were literally driving by our hospital to get to his hospital because they didn't get easy access at ours any longer.

What did he do? Adopt the same policy. So now we've got 30 to 40 percent of the hospitals in North Carolina picking up that policy because we realized by the end of the year the visits in that hospital were down. The complaints were stopped. The satisfaction scores were higher, and the revenue was better. The right person for the right care in the right scenario, and that's why the hospitals in North Carolina are now picking that

up.

Obviously, screening, and I thank Dr. Ballantyne for sharing today about substance abuse is not the only screening mechanism that we need to be doing on those individuals, though, that's part of it. And this study shows, from France, that when it is available, it does help and it does drive down the overdoses. And we are looking at creating more in rural North Carolina, more venues of treatment from buprenorphine/methadone clinics and so forth. That's part of the program.

"She gets her hair from her mom and her eyes from her dad and her drugs from her grandma's medicine cabinet," it's getting risk reduction. It's making sure everybody's aware. Lock your medications up. You take it correctly, you store it securely, you dispose of it properly, and you never share it.

I have a vision that that can just be the same way that we put a seatbelt on in the car, that we dispose of our plastic water bottle in the

recycling bin, that we know what to do with our medications in the appropriate manner. That's got toe driven from the community level so that there's understanding.

We've got released prisoners at a 11.5 percent higher volume of overdoses coming out of prison and jails because their body tolerance is changed. Yet only two counties in North Carolina, thanks to Project Lazarus and others, are now doing education. We now have a certified program from the Department of Corrections to engage all prisons and jails in North Carolina on that education.

One of the things that we did introduce that was shared was our little blue box, the naloxone, Narcan, rescue kit. We're co-prescribing this now in Wilkes County to every individual who's determined to be at risk for an overdose. And that is not necessarily somebody who's got an addiction, though that's part of it. That is not necessarily somebody who has a high level dosing of opioid pain relievers, though that's part of it. But if you have somebody who's on low doses who might have an

obesity situation, who's a heavy smoker, who has sleep apnea, all of those are comorbid situations that a doctor needs to be aware of, and this education is beginning to work.

Project Lazarus is now being in full-force as Operation Opioid Safe, down at Fort Bragg in Fayetteville. They are now giving this blue box to active duty soldiers who are at risk for an overdose because they had soldiers who survived the theater but, unfortunately, came home and died from an overdose from their medication to relieve them of their pain.

They used to have about three people out of 500 in their warrior transition unit dying from medication-related overdoses. The past year, after this has been introduced on base, they've had zero. They've had zero individuals present in overdose because of the education, because of this factor, and when they engage the family, the spouse, the sergeant in the barracks about the issues and the signs and symptoms of overdose, that education has gone a long way to saving lives.

You can see here from a blog from one of our doctors in Wilkes County, "I'm not ready to die. I'm only 26 years old. I always thought people who died from drugs didn't know how to do them right and took too much."

What happened was this young lady went into an overdose. Her brother, who came into treatment in Wilkes County two months prior, had his kit. He took the kit, he took the naloxone, he sprayed it in her nose, and he saved his sister's life. And four days later she got herself into treatment because she did not want to die.

That's the premise of this. None of us can treat somebody who died. But if we can save their life, the avenue is much more wide open for that treatment.

This is our Wilkes County. This is where all this started. That's the little yellow county up top there, about 68,000 people. It stretches up to the Blue Ridge area. Very pretty, very gorgeous. You're welcome to come and visit.

In 2007, we had the third highest overdose

rate in the United States. That's why we had an emergency. That's why we had to do something in Wilkes County. If North Carolina in the United States is at 11 or 12 per 100,000, we reached 46 in little old Wilkes County. And there's other North Carolina counties that are very close to that, but unfortunately, we had the number one listing as the one.

There's a lot of different factors to that, and I don't have time to go into all of that. But there's a lot of factors that have to go into each and every community. And that's what we had to do in Wilkes. We had to address the lifestyle, the culture, the environment of the community and determine, why is there prescribing levels the way they are? And if they are where they are, how can we keep people safe, and how can we stop the diversion of sharing? Because the culture in North Carolina is, you keep it. You don't get rid of it because you might need it someday, or a family member or friend might need it someday. And unfortunately, with the medications today, we can't

do that.

So what has happened in Wilkes County, North Carolina? When we fully initiated this in 2008 and 2009, we had a 71 percent decrease in overdoses in Wilkes County, North Carolina, and that is still continuing today.

(Applause.)

MR. BRASON: Thank you. Yet in that same time frame, our prescribing levels, based on recipients, has not changed at all. The individuals that need the medication, that need the prescription, that have the chronic pain, are not having an access to care problem. They are having access to their medication. But they are wiser. They are taking it more safely. Their prescribers are monitoring and surveillance of their patients. They are using pain agreements. They're using all of those factors. And it is making a difference.

We found, when Wake Forest did the evaluation of our program, they found those pain management agreements, those medication agreements, that patients were more satisfied having that

because to them, it validated their pain with their physician, that their physician was believing and accepting their level of pain that they were describing. And they felt more engaged with that.

So we're very encouraged that the prescribing levels did not have to change, as everybody thought they would, yet we are still at higher levels compared to North Carolina. But I can't say what is over-prescribing because it has to be personalized. It has to be between that physician and that patient if that physician is monitoring every aspect of that patient's life, looking at the dietary and the exercise and the other comorbid situations.

Because we looked at the same venue for the investigation that we were doing, the script levels of those who overdosed in Wilkes County. And on average, 25 percent don't have a script history. They got it from a friend or a family member. They got that prescription from someone else.

But the other 75 percent, in 2008, when we matched the tox screen of that script to the script

that was written by the doctor, 82 percent of those scripts came from a Wilkes County prescriber. 2009, 25 percent, 2010, 10 percent, 2011, zero. Everybody's doing the right thing, best practice, safety measures. Therefore, the right people are getting their medication. They are being taken care of. And those that are seeking the aberrant behaviors and moving away from the system and trying to abuse the system, they can't do that in Wilkes County, which is why we're taking this throughout the entire state, with the total collaboration of all the entire medical community, the state health organizations, Project Lazarus, and all the community coalitions and health departments in North Carolina, to bring about the same changes that we've brought about in Wilkes County that are continuing today.

Our projectlazarus.org, there's a lot of information on there. We are now outside of North Carolina, doing some other state work, and also working with tribal groups and other aspects of the military to address this issue among active duty

soldiers and their families. And I thank you for your attention.

(Applause.)

DR. THROCKMORTON: Our last speaker in this session is Ed Covington. Dr. Covington started the Chronic Pain Rehabilitation Program at the Cleveland Clinic, and has been doing that now since, I guess, 1979, something like that.

DR. COVINGTON: 1840.

DR. THROCKMORTON: 1840, he said. And he's going to be talking from the prescribing physician's perspective. Thanks very much.

**Presentation – Edward Covington**

DR. COVINGTON: Thank you, and thanks for the invitation.

I was asked to speak about the physician's perspective on opioid treatment of chronic non-cancer pain. And actually, the physicians in the country did not elect me to do that, and so I thought I would change it to a physician's perspective and hope it'll be at least somewhat representative. And in that context, I will try

not to whine.

I don't have any conflicts of interest.

By way of background, I've spent 34 years developing a chronic pain rehabilitation program, typically working with patients who are disabled with intractable pain. Most of them have failed appropriate medical and non-medical treatment. And we wean almost everybody from opioids, and we wean everybody from benzodiazepines, Soma, and barbiturates as a part of the program.

We also have an outpatient service which is primary pharmacological, and we treat people there with opioids and adjuvants. But again, we don't use controlled substance sedatives.

I see the clinician treating chronic pain as having a number of conundrums. We rely on published research and lectures from experts at professional meetings. We know that research often produces ambiguous answers, and that certainty awaits study replications and the test of time.

We hope that much of the research will address real-world clinical problems. We expect

that experts will disagree, but that their positions will at least be logically consistent and coherent. And our expectations have not been met.

A data void is easily filled with wishful thinking, marketing, and idiosyncratic practice, and we have a lot of that in the United States now. Despite almost universal acceptance in acute and cancer pain, when I was trained in this field 35 years ago, we were taught to avoid opioids in chronic non-cancer pain because you would have declining efficacy, dose escalation, impaired cognition and alertness, regression, functional decline, and addiction.

We didn't really have any data for that, but we kind of assumed it based on what we knew about opioid pharmacology, and so this was what we taught in our lectures.

Then all of a sudden the rules changed, and the Portenoy study that has been cited earlier was one example of that. I think Ron Melzack's article in 1990 marked a sea change, in which he said people are suffering not because they're

untreatable but because physicians are reluctant to prescribe morphine.

They deliver doses that are too small and too infrequent. When people take morphine for pain, addiction is rare. Addiction seems to arise only if you take it for psychological effects such as euphoria or to relieve tension. And people who take morphine for pain don't develop the rapid tolerance that's often a sign of addiction.

Well, starting around that time, we started hearing lots of medical lectures and seeing lots of journal articles that decried pain undertreatment, which was usually a code for underuse of opioids. There were frequent little remarks about physicians who had been sanctioned or sued by patients because of the fact that they had underprescribed opioids for severe pain.

Medical organizations prepared position statements, some of which you've seen, supporting chronic opioid therapy. State legislatures and medical boards wrote policies permitting and encouraging chronic opioid therapy, and, at least

in California, requiring that it not be a treatment of last resort. And we had a certain amount of education by shaming. If your patients are still suffering, it means you're opiophobic.

Well, this is what happened as of March 17, 1997. U.S. News & World Report decreed that there is no excuse for pain. The doctors have the means to relieve the suffering of millions of Americans, and so the question is, why aren't they doing it?

Well, when a patient brings you this magazine cover, how do you answer that question why you aren't doing it? Is it because you're callous, is it because you're undereducated, or is it because you're opiophobic? So it's kind of hard to explain to people why you haven't relieved their pain.

We were taught in lots of lectures that we had to learn to distinguish pain patients from addicts. We had to learn the difference. But we learned last year that 35 percent of people taking chronic opioids for non-cancer pain have an opioid use disorder by both DSM-IV and proposed DSM-V

criteria. So guess what? It's not so easy to distinguish all the time.

We were taught that opioids have no ceiling, at least in the case of full mu agonists, and the implication seems to be that if the pain persists, you should increase the dose. But we're seeing patients who are opioid tolerant come in for a lumbar fusion surgery and they have no therapeutic window. You can sit at their bedside and give them IV morphine, and their pain will remain 9 or 10 right up to the point of coma and respiratory depression.

We know that opiate overdose risk varies with dose, so that the higher the dose, the more the likelihood of an overdose. So, in effect, there is a ceiling.

We find that morphine equivalents predict return to work in a workers' compensation cohort, and that the people who are least likely to return to work are the ones who are given the highest doses of opioids.

We find that opioid use predicts disability

in back injury. Almost all of our studies, of course, are cross-sectional, so we have to rely on very few prospective studies. But in 1800 workers who submitted lost work time claims for back injury, attempted to adjust the data for pain function and injury severity, it turns out that people who receive opioids for more than seven days are about twice as likely to fail to return to work as the people who don't. So not all is positive.

We're taught that people who have chronic pain don't function well, and the reason they don't function well is not that they're paralyzed or blind, it's because it hurts when they try to function, and that opioids take away the hurt. But, by the way, they still don't function.

Why not? Why is it if you've relieved the pain in a person with, say, mechanical backache, that their function doesn't essentially normalize? And yet most of our studies of outcomes of opioid treatment show little to no improvement in function. My suspicion is that if the function did not improve, the analgesia was probably illusory.

We have the Cochrane review. We've heard some others. This is from 2010. In well-selected patients with no history of substance addiction or abuse, there's weak evidence that those who are able to continue get clinically significant relief. Findings on quality of life are inconclusive. Serious adverse events, including iatrogenic addiction, were rare. But low internal validity ratings indicate that the evidence supporting the conclusions is highly subject to change. The likelihood is high that future studies may overturn these conclusions. So, bottom line, we really aren't very sure.

We were taught that analgesic tolerance is not a problem. Yes, your patients will quickly become tolerant to sedation, but they won't get tolerant to the analgesia. Well, Tony Yaksh back in 1987 had this study of people getting intrathecal opioids -- it was cancer pain -- but you can see there was a very dramatic rise in their requirement for opioids in a matter of 12 or 24 weeks.

More recently, in '01, Doverty showed people taking chronic methadone received almost no analgesia from morphine that was added to it. Again, more recently, patients taking more than 30 milligrams of morphine a day were compared to those taking less than 10 who had orthopedic surgery, they had higher opioid requirements after surgery and more postoperative pain despite the higher opioid doses they were given.

There are frequent articles by anesthesiologists in their literature seeking strategies for how are we going to provide perioperative pain control for the increasing numbers of opioid-tolerant patients that we see.

So I guess, from my perspective, the bottom line is that there's absolutely no doubt whatsoever that tolerance to opioid analgesia develops in a very substantial percentage of the people taking long-term opioids.

Summary of existing data -- a lot of this I'd have to credit Jane Ballantyne with. But at 18 to 24 months, about 50 percent of the people who

are taking opioids will have stopped in controlled studies because they didn't work or they had adverse effects. Twenty percent will have developed problems. About a third will have about 30 percent pain reduction. And a few people will have sustained significant benefit, but we have trouble predicting who those people are.

We've been taught that treating pain with opioids does not cause addiction. Our observations in our chronic pain rehabilitation program is that roughly -- it used to be about 20 percent, then it became 30 percent; this year it's 40 percent of our admissions have a comorbid addictive disorder.

About two-thirds of those had a recreational substance use disorder prior to the development of their opioid dependency, but about a third of them, as nearly as we can tell, had no identifiable addiction or abuse history until they were medically exposed, usually to long-term, chronic opioid therapy.

We're pretty careful; every patient that we bring in we do collateral interviews, so we talk to

the family. And as nearly as we can tell, about a third of the people with addiction really did not have a substance use problem until they were exposed medically.

Well, we have this confounder. Sometimes pain gets better when you stop opioids. And this is a study that we did several years ago of just the people in our pain rehab program who were taking more than 100 milligrams a day of oral morphine equivalence, and they were all weaned off opioids.

We had data on about 45 people, and they were taking a mean equivalence of 460 milligrams of morphine a day. And with opioid weaning, their pain dropped very substantially. Their Beck Depression Inventory dropped from severe to normal, and their Pain Disability Index dropped from severe functional impairment to moderate functional impairment.

Does this mean that all these people got well because we stopped opioids? Not at all, because we had a real shotgun approach. They were

getting cognitive behavioral therapy. They were getting exercises. They were getting adjuvant analgesics: gabapentinoids, SNRIs. They had a lot of treatments combined. But what it does mean is that they were able to get well at least despite opioids. That is, they didn't have to have opioids on board to get better.

In this study, Baron and McDonald didn't do anything but detox. And it's a small number of patients, 23, and they were taking a mean of 554 milligrams of morphine a day. And as you look at the graph, you will see that every single patient who was weaned from opioids in this study had a decline in pain, not an increase in pain.

They were referred to him for opioid wean, so obviously they weren't people who were being real successful. And that's the caveat from both of these studies, that they were done on people who were not opioid responders, obviously.

Well, how does a doc decide what to do in the clinic? You weigh the benefits and the risks. We hope for analgesia, improved function, and

better quality of life, and we worry about toxicity, functional impairment, endocrine and immune changes, addiction, hyperalgesia.

But now they've thrown us a new variable, societal toxicity. So when I'm prescribing a patient, how do I weigh the risks to the patient's granddaughter's boyfriend if she takes it out of the medicine cabinet and gives it to him? How do I put that into my clinical decision making? And I'm not sure that I know how to do that.

Well, in the 2007 National Survey on Drug Use and Health, we found that about 18 percent of the people who were using opioids non-medically got their drug from a single clinician. Other people got them free from relatives or friends or bought it from a drug dealer or something of that sort. So it suggests that a lot of the people who are abusing opioids weren't prescribed opioids, at least not by a single physician.

In prescription pain reliever use in young adults, the 2005 National Survey on Drug Use and Health, we find that only 1 percent of them had a

single prescription from a single physician, and other people were, again, getting them from dealers or from friends or something of that sort.

We have a problem with using opioid research to guide our practice. Research is done with perfect patients, and into our office come people with comorbid substance use, psychiatric illness, poorly explained pain. Research is maybe six months of treatment, and we're asked to provide decades of treatment.

Research is usually with low to moderate doses, and we've often got patients coming on moderate to high doses. Research patients are not taking benzodiazepines and Soma and sedatives and stimulants all at the same time. And in research programs, you've got tightly controlled treatment by experts, and in typical practice you've got loose supervision by non-experts.

What do we have, 100 million pain patients in the United States and maybe 6,000 pain docs? If you figure out the ratio, it's obvious that if pain is managed, it's going to be managed by primary

care physicians, not by specialists. So the risk/benefit ratio is unknown, and we're sort of flying by the seat of our pants.

It would be interesting if there was a label saying, this product has been found to be safe and effective for periods of up to six months in patients taking no other controlled substances. That would cause you to pause, I think, as you read the package insert, and after that, you're off-label.

So what do you do as a clinician when you're unsure of the risks and benefits? You try to select the people most likely to be helped, people with clearly defined causes of pain, preferably nociceptive origin. You try to avoid conditions that are worsened by daily opioids, such as migraine, or conditions shown not to benefit, such as fibromyalgia. And you try to protect those most likely to be harmed, the people with substance use disorders. And you monitor the results meticulously and often.

That's what you should do. What do we do?

Well, in 4 million customers of the Northwest Pacific coast, it turns out that the people who have a substance use disorder are the ones who get the highest doses of opioids, and they get more days supply, and they're more likely to get Schedule II rather than Schedule III, and they're more likely to be given benzodiazepines along with them. So we're clearly using the most hazardous modes of practice with the people who are most vulnerable to it.

So I have to practice with inadequate data because patients can't wait until we have all the answers. And that means the only way to make sense of doing this is to treat every patient as an N of 1 experiment. It seems to me that the literature suggested a six-month trial of chronic opioids is generally pretty benign. Not much bad happens to people in that period of time.

You need to choose wisely the patients that you're going to give opioids to, to avoid multiple reinforcing drugs, to require a contract, urinary drug testing, and collateral information, and to

emphasize medication security and monitor outcomes rigorously.

I think the outcome monitoring may be the most important in this N of 1 experiment. We'd like to see analgesia. We'd like to see an improvement in their mood. We'd like to see activity level increase, minimal adverse effects, and no aberrant behaviors.

Most importantly, if it's not effective, the physician needs to stop. And I think this is, in my experience, where I've seen physicians and patients get into trouble, where a clearly failed treatment was carried on long past the point of obvious failure. And finally, I'd say if you don't know how to land, please don't take off.

Limitations of my recommendations? Well, a lot of times patients aren't started on chronic opioid therapy. They started on acute opioid therapy, and it just never stopped. It becomes prolonged.

So when you see somebody who comes in and they're already taking 100 milligrams of morphine a

day, you don't have a opioid-free baseline with which to compare their progress, so it becomes hard to know if you're helping them, or having no effect, or maybe even being harmful.

If the opioid trial fails, stopping may be difficult, and it may lead to doctor-shopping. And finally, conscientious provision of chronic opioid therapy may require significant amounts of time that may not be compensated in a busy primary care office.

Conclusions. Opioids are miracle drugs for acute and cancer pain. I don't think any of us would dispute that. Research does not exist to inform us about chronic opioid therapy over long periods of time, especially in high-risk patients.

It seems to be helpful for many people with chronic non-cancer pain, but we don't know for how long. When I have this mental picture of a graph showing what happens when you start people with acute pain on opioids, and unless it's a plexus avulsion or a central post-stroke pain, you've probably got better than a 90 percent chance of an

excellent result.

Well, in two years you're probably down to a 30 percent chance of a good result. And if you'd think of the slope of that line, where are we going to be with our people taking opioids for five years or ten years? So we don't know how long they're going to be useful, and we can't predict benefit and harm.

With meticulous prescribing, I think the people who benefit from opioids can get them safely, and those who do not can be protected. Harm to society is substantial; it clearly increases with higher doses. And most societal harm seems to occur to people who never had a prescription, so because of that, the physician very much has a duty to impede diversion whenever it's possible to do so.

Those are the end of my remarks. Thank you very much.

(Applause.)

DR. THROCKMORTON: You know what? In the interest of time, what I think might be most useful

would be to take the break now, and then when we come back, give an opportunity for people to ask the three speakers that we've just heard from as a part of the larger set of discussions that's going to close the day out.

I'm told that we're going to need a little more than just the 15 minutes to get things ready for the next panel discussion. So why don't we start the break now, come back at 3:00, and we'll take it from there.

(Whereupon, a recess was taken.)

DR. RAPPAPORT: Let's get started, if everybody will take their seats. If we could have all the speakers, discussants, moderators up on the stage, please.

(Pause.)

**Full Panel Discussion**

DR. THROCKMORTON: Why don't we start by asking people that have questions for Penney Cowan, for Fred Brason, or Ed Covington, the three speakers from the last session -- if there are things that you'd like to ask them or if there are

other things that any panel members would like to ask them, why don't we start with that. And then after that, we will transition into the broader discussion.

So people with questions about the perspectives that the three of them brought. Please.

MALE SPEAKER: Yes. Hi. Good afternoon. I have a question for Fred --

DR. THROCKMORTON: Speak into the microphone, please.

MALE SPEAKER: Yes. I have a question for Fred Wells. Did I misunderstand all the data that you show regarding the overdoses and the tapering? Did that take into account all the exports from Florida? Because there was, I think -- the Carolinas were the largest export target from the oxies (ph) from Florida.

I wonder how did your strategy, that was all based on the prescriptions that were generated in the county, put a dent on the exports of illicit drugs? Thank you.

MR. BRASON: The situation in Florida with a lot of the pill mills that have been down there have definitely had an influence on not only Wilkes County but especially the western area of North Carolina. And speaking anecdotally to our local law enforcement, yes, they have found -- we had one individual getting $2500 a week just to drive his van down to Florida one time, taking a group of people down there.

Did that influence the overdoses? Possibly within that 25 percent that didn't have any script history. But in Florida and with the laws that they've changed, if your question is, has that been an influence in the drop-off, I'd have to say no because we really haven't seen that drop-off yet from Florida.

MALE SPEAKER: What I really meant is that it seems like the strategies that you had in place were to serve the control of the prescriptions generated in your state, not to mitigate any of the harms that will come from the export of OxyContin from other places such as Florida.

MR. BRASON: I'm still not quite sure I understand what you're asking. But when we look at the overall prescribing in North Carolina, that's not going to reveal any prescriptions that are filled from Florida whatsoever. But we know that it is a factor in the overdoses and a factor in the abuse.

But we're strictly looking at prescriptions by resident, by county, in North Carolina. If they got a script from Florida, that's not going to show up in the data whatsoever.

DR. THROCKMORTON: Over here?

MS. PATTEN: Hi. My name is Christin Patten, and this is a question for any of the three recent panelists and presenters.

There's been a lot of discussion -- I think it's kind of impossible, almost, to extricate the abuse discussion from that of efficacy and safety. But I haven't heard in the last two days any mention of the new tamper-resistant formulations that are out there now. And I'm wondering if there have been any -- has that helped, or are there

tradeoffs on any of those three aspects: efficacy, safety, or abuse potential?

DR. COVINGTON: You're asking has anybody been able to observe a change as a result of the abuse-deterrent formulations? Did I understand correctly?

MS. PATTEN: Yes.

DR. COVINGTON: I know that the price of OxyContin in Cleveland has dropped 50 percent on the street. I don't know data about abuse frequency.

Anybody have that data, of the abuse deterrence?

MR. BRASON: In our location, the opiate treatment program, which has seen an average of 300 in their census, their statement to me is, OxyContin, you can't give it away any more, and most of it is your oxycodones, 15s, 30s, and Opana, are pretty much the drug of choice for those that are finding addiction issues and problems with that, and the requests going into EDs and so forth that that's what they want.

So we have seen, at least in our area in western North Carolina, a definitive difference with the abuse-deterrent formulation for OxyContin versus what it was before.

DR. THROCKMORTON: Go ahead.

DR. DUDA: My name's Lawrence Duda. I'm from Albany, New York. This question is for Fred for the Project Lazarus in North Carolina.

When you have your patient database, when you work that, who enters the information? We're setting that up in New York State now. Does the physician enter each prescription in, or does the pharmacy put that in? And does it run in real time?

MR. BRASON: The North Carolina statute requires every pharmacy to download that data into the database weekly. We started out at once a month and once every two weeks, and now it's weekly.

We're currently working on legislation to get that to not real time but 24-hour. That's about a $54,000 cost every year to do that. But

it's not done by the prescriber. It is done by the pharmacy. It's required. Every controlled substance that's dispensed from the pharmacy has to go into that database on a weekly basis.

DR. PORRECA: I've got a question for Ed Covington. So your stopping rules --

DR. COVINGTON: Stopping rules.

DR. PORRECA: Yes. So tell me a more. Let's say this idea of a trial, and let's say the trial lasts two to three months, and there's a stopping rule, where you're making a prudential decision about whether this treatment is working or not.

In your mind, what would be the criteria that would be applied to decide whether this is a patient for whom it's working or this is not? What we heard on the first day, there's a lot of -- and we've heard throughout, there's a lot of individual variation in treatment response. And I think everybody agrees that chronic opioid therapy, when you start it, it's a trial.

I can tell you, from primary care, the

decision is usually made by the patient whether to continue more than it's made by the physician.

So what are your thoughts on that?

DR. COVINGTON: My thoughts are, first of all, it's important to educate the patient in advance. And I let them know that we aren't going to chase a zero pain level because it really doesn't exist without general anesthesia; that we're going to hope for an improvement in pain, and we're going to hope for an improvement in function.

At the end of six months, if they're not showing some objective improvement, then it's no different than an antihypertensive. If it wasn't working, we would stop it and do something different. It's not rocket science.

At every visit, we get numbers for pain level, pain disability index, so that we know something about their functioning. We corroborate that with a family member so that we know something from the family about their functioning. And then we get some indices of mood and such. So at the end of six months, if they're no better, then it's

obviously a failed trial.

If somebody comes in weight a pain level of 6, and they're spending their live in bed, and six months later their pain level is still 6 but they're going to church and visiting friends and having a life, then I would consider that a successful trial. So it doesn't have to be pain elimination, but I need to see something get better.

**Questions and Answers**

DR. THROCKMORTON: Other questions for the three? Otherwise, we'll throw it open to questions of any kind -- efficacy, safety, whatever.

Mike?

DR. ROWBOTHAM: I just wanted to follow up with that. So if you decide that a patient is not succeeding, what rate do you taper them? And what proportion of the patients do you think just disappear off to another prescriber and are not seen again?

DR. COVINGTON: I can't tell you what percent will drift away. Some certainly do and go

shop for a more agreeable provider.

When we bring people into the rehabilitation program so that we're seeing them five days a week, our standard is to reduce yesterday's dose by about 25 percent. So you get a curve that's fairly steep at first and then really levels off. And if they have trouble with that, we either slow down a little bit or give Catapres or something.

On an outpatient basis, it's not that fixed, and it would probably be something more like 20 percent every four or five days. So we're substantially slower with it. And they basically have essentially no withdrawal symptoms at that rate.

DR. THROCKMORTON: I will ask anyone in the audience that has any questions to any of the members that are on the panel.

FEMALE SPEAKER: (Inaudible – off mic.)

DR. THROCKMORTON: Speak into the microphone, please.

FEMALE SPEAKER: I'm sorry. On the flip side, if you have someone that actually really is

responding with opiates, so you're giving them that six-month window, as a provider you can really titrate significantly in six months. So do you have a ceiling, then, where you would say, okay, I'm not going to go any higher than this amount because at six months we may be flipping?

DR. COVINGTON: The question is, do we have a ceiling? If somebody is showing some benefit at six months, how long do you keep escalating? And I really don't think it makes sense to increase the dose infinitely.

FEMALE SPEAKER: Right.

DR. COVINGTON: And so the question becomes, at what point do you stop? And I start getting anxious at about 200 milligrams of morphine equivalent a day, and at 250 I start digging in my heels.

If I go over that, it's because I've got somebody with ischemic leg pain due to peripheral vascular disease, or they've got something that's clearly objective, nociceptive, that I can see what I'm treating. And then I'll go higher. But I

don't think in the last 20 years, I've prescribed more than maybe 300 of methadone a day, and that was probably to one person, maybe two. So in that range.

DR. THROCKMORTON: And just a second. I'm interested. Jane, comment about that?

DR. BALLANTYNE: Well, I have a slight problem with the six-month -- the idea of choosing a time and then stopping at that time, firstly because, just as pain responses are really variable between patients, so are responses in terms of developing dependence or addiction. You can't necessarily say, well, you're not going to develop any problem in six months, because actually some patients do within six months.

The other issue is, in terms of -- we've already said at this meeting that, quite often, people don't start chronic opioid therapy. They start opioids for something acute, and it becomes chronic opioid therapy.

Especially if the acute phase has been complex, in particular if someone's had trauma or

surgery, it may not be that they have their surgery and leave hospital and that's the beginning of chronic opioid therapy. It may be that they have repeat hospitalizations or repeat operations or things that set them back.

So defining the point at which the six months started is actually not that easy sometimes, quite often, in fact.

DR. THROCKMORTON: And then just one other follow-up.

Susan Horn, I was just wondering, is this the sort of thing that you -- how would your system capture all of the changes that Jane's talking about?

DR. SUSAN HORN: Well, that's just what it tries to do, is to capture all the changes, including the surgeries that the person is getting, which we get in two ways, first because if they are in the hospital-wide system of these multiple sites that we're now collecting the data from, the multiple pain clinics, we will get data downloaded to us. But if not getting it that way, then we'll

get it through the patient surveys.

So we know about those multiple different surgeries they've had both historically as well as more concurrently, and can be putting that into the database along with all the other interventions that are going on.

DR. THROCKMORTON: Thanks.

Andrew?

DR. KOLODNY: Thanks. My question is for you, Doug. I think we've heard over the past two days now that we're lacking evidence that opioids are safe and effective for long-term use in chronic pain.

If on-label indications are supposed to be limited to conditions where evidence suggests that benefits outweigh risks and where evidence tells us that the treatments are safe and effective, if that's the case, should long-term use of opioids for chronic non-cancer pain become off-label, and should FDA let the medical community know that we're lacking evidence that it's safe and effective long-term?

DR. THROCKMORTON: I guess I'm not sure I heard exactly the same thing you did over the last day and a half, Andrew. So I'd be interested in maybe some other people in the panel talking about this.

In general, I think what I heard was that there were individuals that did benefit. There were also individuals at risk for obviously being harmed substantially as well; that identifying those two populations was very challenging given our current database. That was some of the things that we were talking about.

I think that's different than the more, I guess, binary conclusion you heard.

DR. KOLODNY: Well, I think what I heard was that for most patients, we don't have evidence that benefits outweigh risks when opioids are prescribed long-term, that for most patients they may not be safe or effective. I think that's what we've heard, that we're really lacking evidence to make that statement.

If on-label indications are supposed to be

for conditions where we do have good evidence that benefits outweigh risks and that they're safe and effective, should this treatment that we've been talking about for the past two days be off-label?

DR. THROCKMORTON: I guess I'd be interested if the rest of the panel agreed with what you said. I think you said that for the majority of patients, the risks outweighed the benefits?

DR. KOLODNY: No. I'm saying that for the majority of patients, we lack evidence telling us that benefits outweigh risks.

DR. THROCKMORTON: So it's an evidentiary question you're raising?

DR. KOLODNY: Yes. I do think there's evidence, though, that benefits -- or that risks outweigh benefits for many people. But my understanding -- you can correct me if I'm wrong -- is that FDA has to make a determination about these things when considering on-label indications, and that the burden is on proving a treatment is effective and safe if it's going to be prescribed on-label.

DR. THROCKMORTON: I think this therapeutic area is not terribly different than many other therapeutic areas, as I think some of the speakers talked about today, where we've collected information over a certain amount of time for a certain number of patients with a degree of exposure.

We ask questions then about whether or not those data are reasonably extrapolatable when it's hard to get the longer-term information. That's part of the conversation we're having today, is it still reasonable to extrapolate on the basis of what we have, the information, the science that we've heard, about shorter-term use, what we understand about the pathologies of pain, what we understand about the individual responses to pain, the epidemiology, the limited trials that have been done in longer-term. Do those things make us question those inferences we made based on those shorter-term pieces of data?

Again, that's a thing that we do routinely because we understand that, otherwise, medical

products development would halt. I mean, to require that we have randomized, controlled trials that overlapped entirely with the duration of therapeutic exposure for antidepressants or -- you can think of a long list of other chronic medicines. Obviously, it would prevent any new medicines from being developed, which is something I think we wouldn't want to see happen.

So we make informed decisions, and that's one of the aspects of this meeting that I find most important, is to listen to where people are as far as the current information we have available.

Do we need to rethink that?

DR. KOLODNY: I think you're asking a really good question about should opioids be treated differently from antidepressants in some of these determinations. And somebody else raised that point.

I think the answer to that question is, yes, they should, because they are very different. We don't have people shooting pharmacists to get Prozac, so that opioids are highly addictive. And

we have very good reason to be concerned about long-term use, or more reasons to be concerned about long-term use of opioids than other medications.

DR. THROCKMORTON: Thanks very much.

Maybe I can just ask if the panelists want to weigh in as well.

MALE SPEAKER: Again, to put you on the spot, if I may, we've talked about the absence of predictors for those individuals who do well and those people who are at risk.

If we invested Bob Dworkin's 15 million and we identified those predictors, whatever they were, biomarkers, genomic markers, would that go into the label? Would that drive the use?

DR. THROCKMORTON: Actually, you raised the topic that I was hoping that the group would transition to. So the aspect that we haven't had an opportunity to talk about yet today about this whole issue is how to change behaviors.

So assuming that we came out of this meeting with a conclusion that we knew something was

real -- and I won't even say what that was -- what's the most effective way to translate that into a change in behavior on the part of the individuals that are taking care of the patients day to day?

Is it local action, like the Lazarus Project, that's localized to a part of North Carolina, that slowly gets uptaken by other parts of the country as they become productive and successful? Or is it a federal change, say, for instance, to the label that Dr. Kolodny was suggesting, as a way of changing behaviors?

What's the most efficient way to do that? We know that labeling change is a relatively blunt tool as far as changing physician behaviors. We obviously respect off-label uses of medicines. And so it tends to drive one kind of uptake, one kind of change in behavior.

Are there other kinds that might be equally or even potentially more effective if you identified a set of predictors that were really successful at helping you either diagnose more

effectively or decide how to treat more effectively, a genomic test, say, or something like that?

Does that best belong in a label, or does that best belong in a treatment guideline, or does that best belong, I don't know somewhere else? And there are advantages and disadvantages to all of those.

But I'd be really interested in your thoughts, and anyone else's, about how to translate what we learn and hear today to effective change in prescriber practice.

DR. ROWBOTHAM: If I could just comment. I can understand why something going off-label would be proposed because that's something the FDA is empowered to do. But one thing that's clear is that if you take a prescription drug and you take it from on-label to off-label, the insurers are going to say, we're no longer covering it. So what that will do in actual practice is restrict access to patients.

So I'm still kind of wondering how this six

months came about and really what the actual purpose of it is. I accept everything that's said about the lack of evidence and the down side and everything else. I'm not arguing with any of that. But it seems that it's a policy proposal that's tailored to what it is that the FDA is actually empowered to do.

So I'd actually like to hear a little bit more about that aspect of it.

DR. THROCKMORTON: You've got to say more about which aspect?

DR. ROWBOTHAM: Saying six months as opposed to six weeks or three months or --

DR. RAPPAPORT: Where did you hear the six months, Mike?

DR. ROWBOTHAM: Well, no, no. Just to -- I'm looking for examples with other drugs that would go from on label to off label at some time point like six months, and also really just a little more discussion about, really, what is the purpose of that.

Is the goal entirely to try and change

patient behavior? Prescriber behavior? Just a little more background about that.

DR. RAPPAPORT: Well, let me reiterate what Doug was saying earlier, but a little differently. The standard duration of the clinical trial that we require of industry is 12 weeks. That was chosen many years ago because it seemed like a reasonable balance between getting some duration of activity but not making it infeasible to do the studies, too costly, and not having any drugs developed.

However, there are some drugs that are not needed for that long, so the trials are shorter. We do PHN trials eight weeks because that's what we learned from Bob is the right time limit. We do progression of disease in rheumatology for two years to look at radiographic changes because you have to. So there are exceptions.

But if you don't have a reason to go longer or to go shorter, the fallback position is 12 weeks. So we're starting with 12-week trials. To ask the industry to do longer trials in order to get this additional information, we have to have

some type of reason to do so.

It doesn't say in the label, you can only use for 12 weeks, or you should use longer than 12 weeks. It just says it was studied in a 12-week trial. That's all it says. There's no restriction on time use. To restrict time use, we have to have some data to show that there's a reason to restrict time use.

Is that getting at your question?

DR. THROCKMORTON: Let me try again. There are relatively few examples of places where we say use it for a week and stop, or two weeks and stop, things like that. And I can only really just think of antibiotics, and things like that are the most prominent things. And the benzodiazepines have a general warning about taking them too long or stopping too abruptly, those kinds of things.

By and large, we label drugs for chronic use relatively broadly, looking to guidelines, looking at other experience with their use, to help craft how long and under what circumstances those chronic uses should be made.

I think that's one of the things we're talking about today. Is that a paradigm that's still productive here, or is there some reason to change, as Bob had said.

DR. ROWBOTHAM: Can I just add one more comment to that?

So thinking back, really, many years to when deep brain stimulation was used for patients with chronic pain, there was a time period where the FDA -- if I remember this all this correctly because it was quite a long time ago -- said, we want companies like Medtronic and the other ones to provide us with prospectively gathered evidence of how effective this is over -- you know, what proportion of patients respond, or we will remove the labeling indication. That's a device, not a drug. And nothing really happened, and so the label was removed.

But here it seems that you are talking about something that's preemptive rather than saying, we want to see the data, and if we don't see the data by X amount of time, we'll change the label.

DR. RAPPAPORT: No, no. I think --

DR. ROWBOTHAM: I mean, I could just be --

DR. RAPPAPORT: -- you're misunderstanding the whole --

DR. ROWBOTHAM: I could just be misunderstanding the whole line of thinking, but I'm just going by what the discussants, the audience, has said. And I'm just trying to dig into it to make sure I really understand it.

DR. RAPPAPORT: Just to be sure you understand our position, we're saying we can't change the label unless somebody shows us data that convinces us that we should change the label. We're not saying we're going to change the label.

DR. ROWBOTHAM: But that's what's proposed (inaudible – off mic.)

DR. RAPPAPORT: Not by us. There are people in the audience who are asking us to do that.

Yes? So the question you're asking should go to those people.

(Laughter.)

DR. THROCKMORTON: Okay. One, two, and then

I'll be back up that way.

DR. PORRECA: I've got a question about the length of trials. So for NSAIDs, there was about 100,000 person-years of experience in the various trials and about 100,000 people. So I assume that the duration of those trials was a year, on average.

So how was the decision made that NSAID trials should be --

DR. RAPPAPORT: No. The exposure you're talking about is in open label extension studies. That's not the controlled parts of the trials.

DR. THROCKMORTON: In fact, I think, Bob, you could correct me. I think the controlled trials were acute pain models. They were shorter periods of time. And then after approval, there were active controlled trials that were required as a part of the approval, looking at longer-term effects.

MALE SPEAKER: Well, I think the course of the last day and a half make it very clear that there are subsets of patients that are responders

to long-term use of opioids, and there are subsets of patients who have very adverse events to the chronic exposure, and maybe even the acute exposure, to opioids.

I think consistent with the stated FDA goals is to identify ways of stratifying and personalizing the right medication for the right patient. And I think there's now very good knowledge. There's an expanded knowledge of the biology of the opioid pathways to the point where I think, with funding, we can get to algorithms that predict responders, that predict risk with relatively high sensitivity and specificity.

We're very early in that process, but I think there are phenotypic markers that we heard about yesterday. There are genetic variables, which we didn't get to discuss very much. But there are a number of biomarkers that I think, when examined in well-designed cohort studies, can lead to algorithms with very high sensitivity and specificity that will help us predict responders and those at risk.

So I guess my own view is that there is additional need to follow the goals of the FDA to begin to personalize the right medication for the right patient. And this may be an opportunity to do such.

I don't know if that leads to a change in label, but it does mean that there's opportunity to correct this problem, to get out in front of this problem, by beginning to identify those algorithms that allow us to predict risk and allow us to predict benefit.

I guess I'm not quite sure why we don't move forward in that type of discussion, which would ultimately inform the label that would go onto an opioid.

DR. THROCKMORTON: Want to go out to the audience?

MS. FOXHALL: I was going to ask a question on a somewhat different subject, so if you wanted to go on with this -- my question is possibly for Dr. Covington. I'm Katherine Foxhall (ph). I'm a freelance reporter.

We see the SAMHSA data that says that I guess it's the majority of people who have used non-medically in the last, whatever it is, six months, got it from friends and family. But doesn't that include like everybody, even somebody who has used one pill at one time? And do we know more about people who may be the ones who are really in trouble and who are using, long-term, more pills?

DR. COVINGTON: I'm not sure that I know the answer to that, and I wonder if somebody else does. When somebody clicks "Yes" on the -- they used narcotics non-medically, does that mean that I took my daughter's cough syrup one night that was a year old in the medicine cabinet? What's required to get a positive answer to something like that?

MALE SPEAKER: Yes. You're talking about the National Survey of Drug Use and Health, where people self-report. They report use without a prescription or use for the feeling it causes, as the definition of non-medical use.

I wasn't here for the previous presentation.

But it is true that most people say, who are non-medical users in the past year, that they got it from a friend or family. But the bulk of people who report non-medical use are using it only occasionally, and they account, actually, for the bulk of non-medical use.

There are some other people who are heavy users, 200 or more days out of the past year using non-medically, who are much more likely to report buying it from a dealer and on the street.

But it is a broad definition. It does include using it without a prescription for reasons other than the feeling. I mean, if you're using it for pain and you don't have a prescription, that's still a non-medical use.

MR. JACKSON: Hi. Pete Jackson again with Advocates for the Reform of Prescription Opioids.

So I have a question for FDA also. In this workshop, FDA has taken great pains to try to structure the agenda around efficacy of analgesics and not safety per se. And even though some of that discussion has leaked into some of the

presentations, especially today, I'm still concerned that that's a significant chunk of the information that constitutes evidence on which drug approval decisions are made. And since that's not really been directly, explicitly addressed by FDA in this workshop, I'm wondering if FDA would consider holding a similar workshop where that was the focus, given that it would probably bring in a bunch of additional experts and require another workshop like today.

DR. THROCKMORTON: Yes. Thanks, Pete. It's an interesting question. We did specifically focus this workshop on efficacy because as we looked at the meetings that had been held in the past, the discussions that we'd been a part of, that hadn't been the central focus of any meetings that we had participated in to this level of detail.

On the other hand, as you know, we've had a variety of opportunities, and you and I have had a variety of opportunities to talk together, about the safety and the misuse and abuse of opioids in other settings.

So we had -- the FDA, perhaps selfishly, we felt we had had reasonable exposure to the large discussion about the misuse and abuse of opioids from other settings, and that what we needed to do was focus one meeting on what was known about the efficacy of opioids in chronic non-cancer pain.

Now, when we go back and we talk internally, it may be that we'll come to the same conclusion you're suggesting, that is, that we need to bring together a group to have a targeted discussion like this around the safety of chronic opioid use.

This is the beginnings of a discussion. For us, we need to start with the science, understand what we know and what we don't know, and then decide what the best tools are to help address the issues. And I take your point.

MR. JACKSON: Okay. Just to make the point that safety is part of the science as well. Bob mentioned that you can't change a label without evidence, and safety evidence would seem to be part of that equation.

DR. THROCKMORTON: I'm not disagreeing it's

an important part. It's just that we've had other opportunities to talk about it. If there are things we still need to discuss, then we need to do it.

All right. Let me see. I've got a question here.

Oh, I see. Please ask the speakers to identify themselves.

(Laughter.)

DR. THROCKMORTON: I think there's a comment over there.

MS. REED-HOLTUM: Yes. Lexi Reed-Holtum again, the Steve Rummler Memorial Foundation. Thank you all for being here today. There are a bunch of brilliant people on the stage, and I hate to keep focusing on you two gentlemen in particular.

But I'm just curious again about the labeling question. If I heard correctly, Bob responded that the FDA isn't going to change the labeling until something's proven unsafe. And I just don't understand how you can ignore the

escalating overdoses and death.

I heard your response as kind of like how the tobacco industry ran things for a while, that something was allowed to be continued to be used because it wasn't proven unsafe, when indeed it is. And I don't see how you can overlook that evidence.

So sorry to keep harping on this, but the response was really troubling to me.

DR. THROCKMORTON: It wasn't intended, I think, to be troubling. And the piece, I guess, we're at is talking about that very last part of your construction with the tobacco industry. Do we know, in fact, that it's unsafe? It's back to Andrew Kolodny's comment, do we know, in fact, that the benefits fail to exceed the risks for an identified population as identified on the label?

You've articulated before -- I think others have articulated clearly -- you believe that to be the case.

MS. REED-HOLTUM: I guess we don't know it to be safe. So you're allowing something to be out there that we don't know to be safe. And how is

that you protecting our society in the way that you're supposed to be?

DR. THROCKMORTON: You understand this is something, of course, that -- what we need to do is to be able to say we look at all of these things carefully. You have a point of view. Others have a point of view. I think what we've heard in the last day and a half, that there are other individuals that believe that there are identified populations where the benefits do exceed the risks.

So there is that tension between what you've concluded, based on your looking at the information that's available, and what others have concluded, based on their looking at the information.

The FDA's in the middle. Our job is to protect and promote public health, as you said. That requires us to listen to all sides, come to an agreement, come to a decision, and then act on that decision. That's the place we are now. It's in that discussion. It's understanding the nature of the available data and understanding what the best next steps are.

DR. BALLANTYNE: I just wondered, since we're asking you the questions now --

(Laughter.)

DR. BALLANTYNE: -- whether you could inform us about other mechanisms than labeling changes, for example, black box warnings. Since we do have some data on several safety aspects, not just -- and I know you don't want to focus on abuse, and that's a very hard thing to quantify, but death from people with sleep apnea is not that hard to quantify. And the correlation between high doses and some of these adverse outcomes in pain patients is not that hard.

Is there some way that you could at least warn people?

DR. RAPPAPORT: First of all, there are boxed warnings on all of these products that have some of the most extensive warnings in any medications, warning against a number of issues: respiratory depression, addiction, and all of those things.

If there are additional things that should

go into the label, we can do that. Again, all we need is to have an appropriate amount of data to support making that label change. Making a label change for safety is far easier than to put something in that says that this doesn't work after X number of periods without data. Safety, we always make label changes that are appropriately supported by data.

Now, if you think that there's enough data to support making a label change for people with sleep apnea, we would certainly consider that. All we need is for somebody to provide that data to us.

We don't have the time to spend just constantly reviewing literature to look for problems. But if there is a problem that you think's not addressed in the label in terms of safety, absolutely we'd want to know about that.

DR. BALLANTYNE: I appreciate that the dose issue is really difficult because you're labeling to individual drugs, and what we're seeing is dose issues related to maybe multiple opioids or multiple substances. And then the real problems

are polypharmacy. That's difficult.

But most of the studies are looking at morphine equivalent dose. I just wondered if there's any way you can put that in, that for any patient taking any individual opioid, if their morphine equivalent dose exceeds safety levels, is that something you'd put in?

DR. RAPPAPORT: Well, you have to again show what that safety level is for that drug. And, as you say, it's very confounded by a lot of other issues, polypharmacy, and where do you make that cutoff so that you're providing adequate safety information but you're not limiting patients who actually need higher doses? Certainly you've seen patients who need markedly high doses.

That's a tough one. Again, we would be the first ones to jump on putting something in the label if we had appropriate data to really show that there is a threshold level for a particular drug and that it's not confounded by the other issues.

DR. BALLANTYNE: Actually, the number of

patients that need high doses is very small. The most patients that do well do well on much lower doses. So I agree there are a few outliers, but also, whatever you do in terms of labeling doesn't preclude exceptional patients getting the drugs.

DR. THROCKMORTON: Still need the data.

DR. COVINGTON: I hate to be grilling you, Bob. Tell me if I'm wrong, but it seems to me that there is pretty much universal consensus that the effect of acute opioids differs from the effect of the same opioids after 24 months in a way that's not true of beta blockers and ACE inhibitors and nonsteroidals and things of that sort.

Is that not generally accepted, that whatever the efficacy of chronic opioids is, it's different than the efficacy of acute opioids, which is what I consider a 12-week study?

DR. RAPPAPORT: I don't know if I can answer that. I'd like to hear from (inaudible – off mic.)

DR. THROCKMORTON: Where are you taking that?

DR. COVINGTON: I guess where I'm taking

that is you raised the question of what would serve as a signal to indicate that this drug needs some sort of extra research outside of our normal 12-week default. And it seems to me that what would call for that would be convincing evidence that the effect of the drug at two years is somehow different than the effect of the drug at 12 weeks. And do we not have that?

DR. RAPPAPORT: I would love to hear the answer to that question if anybody has an answer to it. Or do you think that we don't have an answer?

DR. DWORKIN: I'll answer your question with at question. Do we have any evidence that the effect of amitriptyline in either neuropathic pain or depression is the same within three months after initiation of treatment as after two years? I don't think we have that evidence for any of the drugs that are used for any type of pain.

It's a great question, but I just think it's not only opioids that are lacking that evidence, it's everybody else you prescribe.

DR. COVINGTON: We don't see people taking

3 grams of amitriptyline (inaudible – off mic.)

DR. THROCKMORTON: Mike, do you want to comment on the evidence on tolerance?

DR. ROWBOTHAM: I've gotten myself into enough trouble already.

(Laughter.)

DR. THROCKMORTON: I know I've had lots of conversations over the years with what exactly is the solid evidence of tolerance that we have.

DR. ROWBOTHAM: So we've done two studies where we looked explicitly for tolerance. We have another study which hasn't been published yet. One was a healthy volunteer study, where subjects got an injection of morphine, two injections a day, for five days. And the first four days were either morphine or placebo, and then they switched to the other one.

At the end of four days, we saw a little bit of a trend towards a reduction in the analgesic effect, and definitely fewer side effects by then. So there really wasn't clear evidence of tolerance over a four-day period in healthy volunteers.

When we were doing the levorphanol study, we looked at the last two weeks of therapy. And that was an eight-week study to see whether or not subjects were starting to escalate their dose, or to see a deterioration in their pain control because the number of capsules the subjects were allowed to take each day was under their control within general limits.

What we saw was that pain scores were as likely to go up as down in the last two weeks, and the number of capsules they were going to take was as likely to go up as down. So we didn't see any clear trend there, either.

So part of the reason why I was pushing back on that six-month issue is, how would we even figure out what the appropriate time point is? I completely agree with Ed that you're not seeing patients taking 300 milligrams of amitriptyline. One, they wouldn't still be walking at 300 milligrams because the toxicity is there no mater how long you take it. And so opioids are really a rather unusual category of drug, in that there's

enough tolerance that you can keep escalating the dose.

The benzodiazepines are another one like that, too, where patients, over time, can escalate themselves up to just enormous doses. But with opioids, it's a really important question to figure out what is the time course for this tolerance? How much variability is there from one person to another? And can we incorporate that information into how to rationally manage these medications?

DR. WOOLF: My question sort of relates to that, which is really back to the practice-based evidence, observational studies, which obviously can provide some of the information we're looking for.

The question is, given the heterogeneity of the populations and their responsiveness to treatment, both in terms of efficacy and adverse effects, how many patients will we require? You've got a thousand patients, you mentioned.

It seems to me we're going to need hundreds of thousands of patients if we're going to get very

strong associations where the false positive rate is reduced because you're making so many measurements -- the Bonferroni factor is such that to get statistical power, you're going to have to move from small cohorts to enormous cohorts.

I just wondered if you had any sense of what kind of power would be required to identify these subsets of patients who are either at risk or who benefit, or who become tolerant until not.

DR. SUSAN HORN: I think what will happen over time is that you will be looking at these characteristics of patients in subgroups that we'll set up already. We probably won't want to answer this question in a global sense. We're going to want to do it in a much more personalized sense.

So it will really depend upon what clinicians and even patients would tell us of where they feel that things are working and where things are not working, and then we can look at the data to see how much is supported and for how long in that regard.

But I would think that -- the sample size I

can't quite tell now because it depends upon the number of different factors that we're going to be looking at. It's not something you can answer generically. But we're going to be able to get some indications, I think, in the short run that we're going to lead to trends, and then in the long run we can see whether those are confirmed or whether there are other confounders that will change the associations. And we'll go in, then, splitting off different subsets of people.

Because it does sound like, from all the things that people have been saying, that this is going to have a lot of personalized and person-specific factors that are going to influence success or lack of success. And it's not going to be a global solution. It's not going to be six months for everybody or two weeks for everybody. It's going to be much more patient-dependent.

DR. THROCKMORTON: I'm going to go out to the audience, if that's all right.

Oh, a short comment.

DR. GALLAGHER: One more comment. I'd like

to follow that up because I think Michael Von Korff presented data on his consort cohort where he identified 61 percent of a group of patients who are dosed under 50 milligrams a day of morphine. That's a substantial number of people who seem to be on long-term morphine and doing well, going to work.

It reminds me, to make a translational comment to Frank Porreca's comments earlier, about the rats that took enough medication to keep the pain down, and then went about their business eating and going on their wheels and going back to work, so to speak.

I think we're going to find, even within mammalian species, differences, but also within the human species, very different responses to these drugs. So I think "one size fits all" does not fit this huge, 100 million population. We're going to see a lot of variability.

I'm delighted to hear about your study and these large cohort studies because they're going to really make the difference in populations.

DR. THROCKMORTON: Thanks. Let's go out to the audience. Thanks for being patient.

MS. NAGLE: Hi. Sure. It's Becky Nagle from ESI. One of the things -- you asked about the duration, is there any drug that's limited by duration. And one thing that comes to my mind is metoclopramide. Metoclopramide was recently changed, maybe in the last few years. You're not supposed to use it, I believe, for more than 12 weeks.

It's interesting listening to this debate the last couple of days because it's very much like guns. People are pro-gun, anti-gun. And we seem to be focused on the label, like the label dictates practice. And it doesn't. Okay? The FDA might think so, but people use Reglan much more than 12 weeks all the time, even with that information.

So you have to recognize that changing the label is not going to change the practice. There has to be more oversight of practice. And you can't compare opiates to tricyclic antidepressants, not only because of the lack of a ceiling effect,

or whether there is or not, but that people don't sell amitriptyline on the street. The only drug that I know people are really selling on the street is HIV meds. But you can test somebody and know if they have it or not. You can't test pain meds.

So the best way to change this is education and oversight, which we don't typically have right now, with doctors prescribing poorly and patients not being followed afterwards. And I think that we need to not focus so much on the label, but think of that you can change the label, take some drugs out of other people's hands, and they're still going to get them.

In the North Carolina example, they just went to the next county. As soon as you change one rule, they go to find another one. People with real pain, mental or physical, need treatment, and no one ever talks about that.

DR. THROCKMORTON: Yes. I don't think anyone with the FDA was trying to say we knew that labeling changes that people had been proposing would solve the problem. It is one tool. It's not

as though labeling doesn't have an important function; it does drive certain aspects of use. Absolutely true.

I've now lived through several attempts to modify behavior through a labeling change. Cisapride was the drug that I tried very hard to save through labeling changes. It had a very targeted, very identifiable safety signal, and some efficacy. We could not modify prescribing behaviors despite our best efforts, and we had to remove the drug from the market.

So no, I understand pretty well the limitations. On the other hand, I do agree that there is value in the labeling. I see it as very important as far as communicating things like safety information, where you have that well in hand. So I don't want to sound as though I'm a nihilist.

MS. NAGLE: No. And I don't mean to minimize the value of not having the label. I use the label to help twist people's arms every day. But that doesn't twist them enough to change.

DR. THROCKMORTON: I think it's one tool. I had tried to transition the discussion here a little bit to that. It's how to choose the right tool. What is the right approach to make the changes in prescribing behaviors that we all see as needed? Is it labeling or is it something else? Is it a treatment guideline? Is it some other intervention? Is it the Lazarus Project mandated by every state legislature across the country?

There are a variety of tools that have been proposed for intervening in the issues around safe and effective use of opioids. I don't know what those right tools are. That's part of the conversation we're having today. And I welcome conversation about what's the right tool here, and anyone that has a view on it. Thanks.

DR. PORRECA: Our health plan cut the percentage of patients on high-dose regimens from 18 percent to 9 percent over a four-year period by a shift from a culture of I think over-optimism about the efficacy of long-term opioid therapy to a stance that is more similar, a more balanced

perspective, of the kind of what we're hearing today in the presentations.

So I think what the label does is it influences what people are able to say about the effectiveness of the drug. I don't think the label is particularly important. I do think the culture, the practice culture and the oversight, is very important.

What I heard today gives me a lot of optimism that the practice may begin to shift in the direction suggested by the evidence that we have. But I think that's where we should be focusing our attention, is how can we change the culture of practice so that it's in conformity with what we know about making practice as safe as possible and as effective as possible?

DR. THROCKMORTON: Thanks. We'll go over here.

MALE SPEAKER: CHAUMONT: I promise this is my last one. I am very privileged to be here in this consortium advancing pain therapies. But I can also trial you that the mayhem --

DR. THROCKMORTON: Speak into the microphone a little more, please.

MALE SPEAKER: -- that the mayhem that it has left behind, the advance in pain therapies, has also been disastrous. I can tell you that it's great to have phenotyping research to identify patients. But I am in the trenches, and I see this day in and day out. And we have already markers of risks, and I can tell you that nearly all of the Florida deaths are due to prescription opioid medication concomitantly prescribed with some sort of central nervous system depressant, either carisoprodol or Soma, some gabapentinoid, or alcohol, or marijuana, or some other drug, psychiatric medication, Seroquel, for instance.

So the recognition of the research and those studies that point to the safety isolate patients and select for those patients that are free of drug addictions, of substance abuse, or that are free of dependence or concomitant use of other drugs.

But that's not what I see in my practice. What I see is completely different. And I think we

can stratify and quantify those risks just simply by looking, what are you taking?

The other issue is, what is the aberrant behavior? And that's a very difficult question because, obviously, you cannot quantify it, either. I can quantify it, and possibly with a great deal of bias, but at least I am there, dug in the mud up to my nose taking care of these patients.

So I just wanted to point out to you that we don't really have time to wait to discover which genes are going to respond favorably to opiates while other people are dying, and that we need to take some shortcut, albeit not perfect, to try to put a stop to the bleeding.

Thank you so much for having me here today.

DR. THROCKMORTON: Thank you.

MR. TERMAN: I'm Greg Terman from the University of Washington. Is it okay to ask questions of the people sitting down up there? Maybe to Bob Dworkin.

So if you had $15 million, it's pretty clear that a lot of the studies maybe stop early, and

there's not much in terms of evidence of efficacy out many months or years. So how long would you suggest to people in the audience that are going to do a study to look -- how long would you look?

Raj suggested a year. I guess 12 weeks isn't good enough. How long is good enough?

DR. THROCKMORTON: And the goal of the study is to decide whether or not --

MR. TERMAN: Efficacy.

DR. THROCKMORTON: -- they still have analgesic properties after some longer period of exposure?

DR. DWORKIN: So, Greg, what I would do is a randomized withdrawal with patients who were on opioids for, say, two to four years. So we'd find patients who were on opioid analgesics. Hopefully it's relatively stable doses for several months.

Then we'd withdraw them on a completely double-blinded basis to placebo, probably an active placebo to mimic some of the opioid side effects like constipation, Lomotil, Imodium, or they continue on the same dosage of the opioid. And

then I think there'd be an interesting discussion about whether you have a third arm where they, again on a double-blind basis, get another medication.

So I would personally do a randomized withdrawal to see if, in patients who've been taking opioid analgesics for several years, there is efficacy at that point. That was one of the buckets this morning.

DR. THROCKMORTON: Let me just say that in other therapeutics areas, when these similar questions have come up, randomized withdrawal study designs have been ways that people have approached this successfully.

So deciding whether or not antihypertensives work in children, which is -- you can only leave children untreated for a certain period of time. That's done by mostly a randomized withdrawal population trial design. They are short. They are controlled. They are safe. The challenge here, as I understand it from Bob, is the patients are habituated. They may be --

DR. WOOLF: It would be blinded to the withdrawal because of the withdrawal symptoms.

DR. DWORKIN: I would make sure that the taper was long and slow, and do our best to blind it that way. So a very slow reduction in the dosage of the opioid over a couple of months, and with the placebo group, the group that's being withdrawn from the opioid, getting an active placebo that's going to ensure the integrity of the blind. And I would use something like Lomotil or Imodium at a small dosage.

I think Mike was the person this morning who mentioned the possibility of having a third arm, where they could be withdrawn from the opioid and initiated on another treatment. Then we could have interesting conversations about what the active comparator arm would be.

I think this is a trial that no academic investigator could do without a lot of support from the National Institutes of Health, support being funding. I think I already said that this morning in a different way.

DR. TERMAN: Could I follow up on that, then? Do you think you could do it with the normal five-year R01 sort of mechanism?

DR. DWORKIN: Yes, Greg. I'm glad you asked that. The kind of normal R01 model for that is exactly a six- or seven-year study. And what I feel strongly, based on the last day and a half, is if we really all believe this is an urgent public health question, then we don't use a six-, seven-year, eight-year R01 approach, but that one of the institutes at NIH decides to take the lead and get this done in two years.

I think that the study I just described can be done -- I don't know whether it's 15- or 20- or $25 million, but I'm sure that it can be done in two years. And so I would not use a typical NIH mechanism to address this issue if we all agree, and I think we all agree, this is an urgent public health need.

DR. THROCKMORTON: Other comments on that? Otherwise, we'll go out to the --

DR. BALLANTYNE: Well, I think I was telling

Bob this morning that, actually, in the old UW program they did something similar, not as a trial -- but that was just the clinical practice -- was to do blind withdrawal and to do it in a rehab setting. And sure enough, you can achieve remarkable results.

The patient's pain improves and they stabilize, generally, for about a year. But unfortunately, quite a lot relapse. So I just wondered how in your design you would follow up more than two years? Because I think they tend to relapse years later, not necessarily within months, but within years.

DR. THROCKMORTON: That was why I asked the question I did, which is what the goal of the study would be. If the study is to decide whether or not there are still analgesic properties out a year or two years after exposure, then that's not a question the trial would be addressing. It's an important question to ask.

The trial would be, does the pharmacology -- is there still that analgesic

property? A separate question for follow-up would absolutely be, what are the consequences of bringing some --

DR. RAPPAPORT: You can do an open label follow-up and follow them to see if they relapse in terms of the problem.

DR. THROCKMORTON: Go out to the audience.

FEMALE SPEAKER: First of all, I want to thank you, FDA, for holding this, and maintaining a very balanced discussion, and being very fair about hearing every point of view. So I really appreciate this meeting.

DR. THROCKMORTON: Could you speak into the microphone? It's hard to hear you.

FEMALE SPEAKER: Yes. So you can hear the thank you. Anyway, I was thanking you and also saying I appreciate your focus on efficacy and long-term studies.

But I had a question. Really, it's for, I think, Dr. Woolf and I don't know the name of the fellow in the back that was talking about stratifying and looking for biomarkers and

phenotypes so we could really get better at deciding who these medications were good for.

If you had the $15 million, you researchers, could you get there? And, as a follow-up to that as well, could we not look at people who have done really well and, of course, people who haven't, and would studying them help you?

DR. THROCKMORTON: Do you want to start?

DR. WOOLF: In a sense, that's exactly why I was asking that question of how many patients would be required to identify those subsets of groups which one could analyze, at least genomically. So I think that is a very valid response.

But one wants to be sure that you are getting the right subsets and, I think, Bill made a comment about having to cluster them together and to make sure that those clusters are actually real. And it's a non-trivial problem.

MALE SPEAKER: It's a very (inaudible – off mic.)

FEMALE SPEAKER: What about the 15 million question? If you had $15 million, could you solve

it?

MALE SPEAKER: We could go a long way.

FEMALE SPEAKER: Because as far as I'm concerned, we're lacking the research that really is needed. I feel like we're back in the days of cancer, like 50 years ago, when everybody thought cancer was one disease. And I think what we're talking about with pain is a much more complicated picture. And the money really needs to be focused on research so that everybody has good outcomes. So thank you.

DR. THROCKMORTON: Bill?

DR. MAIXNER: I think one of the ultimate goals would be to develop methods that have high positive and negative predictability for efficacy and for predicting safety, however that's defined.

So the goal of developing algorithms for prediction using various biomarkers would be the goal. And I'm of the impression that it'll take a little bit longer than two years, in my view, to do this.

The approach would be to use both phenotype,

as Clifford mentioned, to cluster patients into the different subpopulations at baseline and then follow them prospectively over whatever that time period is, a year, two years, whatever the definition of time point is. And then also, within the context of that, to look at, I think, genetic biomarkers that would predict response as well as adverse event, such as tolerance and potential propensity towards addiction.

There are I think examples emerging in the pain field where this is going to prove to be feasible for development of algorithms, for the development of chronic pain conditions. And I think that these same types of algorithms could be put forward for drug response.

I don't think it's going to take 100,000 patients to make sense, especially if one uses phenotypic markers with genomic markers. We now know that the so-called effect size of the phenotypic markers and the effect size for prediction of whatever the endpoint is of the genetic markers will determine, to a great degree,

the actual population size needed for these studies.

I think phenotypic and genetic markers will have sufficient effect sizes that within a couple thousand to 4- or 5,000 patients should be sufficient to develop algorithms which have, I think, reasonable sensitivity and specificity to make predictions.

DR. KOLODNY: Andrew Kolodny. A label change may or may not have a direct impact on physician behavior, but it would have an immediate and direct impact on pharmaceutical company behavior because a label change would prohibit drug companies like Purdue Pharma from marketing OxyContin for chronic non-cancer pain.

To the extent that you believe that marketing leads to over-prescribing, then by making a label change, you would potentially decrease over-prescribing.

A moment ago, Bob mentioned that we believe there's a subset of patients who do well on long-term opioid therapy. But does a subset of patients

justify an on-label indication? Many psychiatrists will agree that there's a subset of patients with severe treatment-resistant OCD who benefit from the addition of an antipsychotic. That doesn't mean we would allow AstraZenica to market Seroquel for OCD.

Maybe you could just inform us about on-label indications. Is the fact that a subset benefits from a given medication reason to make that indication on label?

DR. THROCKMORTON: I think I don't want to make this meeting today a conversation about labeling. But, in fact, subsets are sufficient to get labeling. A salient example is the oncology community, where very small fractions of individuals for some approved medicines, in fact, have response rates, and yet obviously for those patients they're highly effective and, in fact, the products are approved for broad indications.

But I take your point. You want to be able to describe the efficacy of a product for the broadest populations that the data can support. And to the extent that you can bound inappropriate

use by pointing out demonstrated safety concerns, obviously that's something that we all want to do.

The question is, how do you find that balance? How do you find the balance between the group of individuals that are going to benefit, that you have evidence that you believe constitutes proof that they would be benefitted from the use of it, while preventing the unfortunate or the bad outcomes because of either inappropriate use you're suggesting, because of prescribing that was more enthusiastic than maybe it could have been.

It's a real challenge. It is data-driven. As I said before, I think it begins with understanding really carefully the nature of the data, both in terms of efficacy and, Pete Jackson, as you suggest, in terms of safety. I think that's an important first step.

FEMALE SPEAKER: Thank you. Thank you for this great discussion.

As the FDA defines the use of opioids, the benefits, dependency, or addiction, is there concern that describing behaviors will be a step

towards a psychiatric label?

For instance, right now the lumping of chronic pain patients who are seeking health care frequently by the American Psychiatric Association has a new label in their DSM-V that we have just a short window to respond on of "a complex somatic symptom disorder."

I'm hoping that as we have this discussion, that we maybe have a sensitivity to the related spinoffs that will affect people with chronic pain as we go forward. And I hope that somebody can speak to this a little bit.

DR. THROCKMORTON: In a general sense, the FDA recognizes the value of individual patients and individual physicians making decisions for those sorts of things. We tend to draw back from trying to describe complicated social situations like that because we recognize things change. Definitions change. We used to think cancer was one disease, as someone said. Obviously, now, if we had started approving drugs only for cancer but not broken it out, that could have been a problem for us.

So I'd say in general, we try to be as careful as possible to describe the natures of the benefits without stepping into places that we expect could well change as science evolves, or something like that, and be ready to change if new information comes up. But I think we understand that a label can be too prescriptive as well.

FEMALE SPEAKER: Thank you. I wasn't so concerned about the label, just as the general definition of the use of opioids coming out of this great conference. I think that there are concerns of a mental health label, and I hope that we can either step in front of that as we see that happening and respond to it. So thank you very much.

DR. THROCKMORTON: Yes. I'm sorry. And I didn't understand. In fact, HHS, there is in fact an effort going to harmonize, to the extent we can, some of the definitions that we've been using around abuse, misuse, and addiction because we recognize that those definitions and the ways that we use them could be different from the definitions

that are used in the DSM or something like that. And Bob and some people within the FDA have been leading an effort to try to do that, and we're starting a conversation with HHS as well.

MS. RUMMLER: Thank you. This has been a very interesting, informative, and helpful session. My name is Judy Rummler. I'm with the Steve Rummler Memorial Foundation. And my question is for Len Paulozzi.

The CDC published some facts about this epidemic in November of 2011, and the first fact is that the quantity of prescription painkillers sold to pharmacies, hospitals, and doctors' offices was four times larger in 2010 than 1999. Another fact is that nearly 15,000 people die every year of overdoses involving prescription painkillers.

Isn't this evidence of something? We're searching for evidence, but it seems to me that this would be evidence that these are not effective in the way they're meant to be effective.

DR. PAULOZZI: Thank you for that comment. You are, of course, correct in your statements, and

I don't think the situation has improved since that publication in November. If anything, it seems much worse.

That doesn't relate to the question of effectiveness; it's on the safety side, of course, the comments that you made. I guess I'd only put that in context and say that, well, we're 20 years into this epidemic now, and we have perhaps 16,000 deaths a year where opioids contributed to or solely caused the death.

We had deaths in people who would not have died of drug overdoses at all, populations, states, demographic groups who have not been affected by drugs in the past. So we're paying a terrible cost for widespread, chronic, heavy use of opioid analgesics in the United States.

So if we're getting a benefit from it, we really need to establish that soon. We can't wait because our country, unlike any other country in the world, is experiencing tremendous costs from this. So if there's a balance there, I think we need to establish what the benefits are. Is our

country better off because of this, or are we just paying costs?

MS. RUMMLER: Thank you.

DR. CARR: Dan Carr, Tufts University. This is just a comment that echoes features that have already been emphasized.

The first comment is to again thank the organizers of the conference and the participants for an outstanding experience in the last couple of days.

The comment concerns my sense that there's a wonderful opportunity that has not quite been crystallized or articulated to take the crisis, which is at a public health level and involves individuals who would not be entered into a trial -- namely, those out in the community -- and how to advance the clinical trial methodology and public health methodology to try to have a concurrent assessment of impact in the public's health from prescribing patterns or conclusions that would be reached, having enrolled patients who would themselves be the unit of analysis in a

conventional trial.

So I think that thinking back, let's say, to the '60s, my understanding is that that's when several people altered or helped work with FDA to alter the whole structure of clinical trials, to move from just safety to safety and efficacy, phase 1, phase 2, phase 3, and so on.

I have a feeling that in the time since the '60s, advances in informatics and data gathering have actually presented data, much of which we've seen in the last two days, which were not possible to be captured 50 years ago, 60 years ago.

So my sense is there's still a gap in what I've been hearing because there's an obvious recognition of public health impact of opioid prescribing that will not be assessed, no matter how sophisticated the trial is, of individuals who have pain who are given opioids, the outcomes of which will inform therapy or label.

So it's just a comment. I think it's a terrific opportunity. There are also methods that have been employed to study and quantitate

connectiveness and community effect of interventions on other individuals.

Just as a passing thought, perhaps that type of thing could be embedded in current regulatory frameworks by expanding the notion of the environmental impact statement of a drug. In many instances, environmental impact is assessed by trying to see how much more diclofenac gets in the water supply and influences trout if you add X number of tons per year. But more broadly speaking, the types of things you've addressed from a public health perspective could be construed as an outcome that affects the environment. Thank you again.

DR. THROCKMORTON: Yes. I couldn't agree more with the interest in using novel electronic data capture, databases, and those sorts of things to try to expand our understanding of the efficacy here, the safety here, efficacy and safety writ large in all therapeutic areas.

I wonder, do you have a worked example of a place where people are using that? So the

Geisinger experience, for instance, is very provocative to me. That's the kind of integrated healthcare system and electronic data capture that you might point to and say, there's an opportunity to use their electronic health record in some way to understand better the efficacy of these medicines.

I think we all look at those kinds of things and say, that's terrific. We want to get there. The question is, how do we do that? How do we make that step?

DR. CARR: Well, there are many examples of electronic health records and things proposed. What I would say is, take your analogy. I would say, what should be done in the trial is, hypothetically, if something were done to implement the treatment algorithm at Geisinger to capture misuse, abuse, mortality, return to work, economic status of the community, which would include individuals who are not automatically being captured because they're participants in a trial.

So I'm looking more at a social

connectedness like a Christakos model. I know that some people have commercialized that; I have no interest in any of those commercial things.

But I think that what we're seeing here is a coalescence or the imminent coalescence of analyses at different levels of scale. And it's a wonderful opportunity, but I think we are uncomfortable because those of us that are accustomed to doing the genotyping feel comfortable at that level. And it's not their job to figure out the community, and that stuff sounds fuzzy and ill-defined anyway. And those who deal with sociology or global health care budgets of the U.S. and so on are not comfortable looking at a very micro scale.

By the way, let me also mention that not only should the model change according to spatial scale, but I think as we've discovered, time is another dimension. And experiments that work well in one dimension and give us a strong response just fail to predict. And we've kind of stumbled upon that now, and we're scratching our heads, saying, gee, we failed to predict what happens in a long

time frame.

But basically, my point was, I think there's a terrific opportunity because one is hearing from different quarters the impact of opioid therapy for good and bad on an individual basis and also on a community basis.

So I would urge that when you take that 15 million, you take a portion of it and try to use existing models, which are actually feasible and are being used, if they're available commercially, to study the impact of the prescription upon the public health consequences such as rate of fatalities or poisonings and so on.

DR. THROCKMORTON: It's a terrific idea. I don't know, Fred, I seem to remember Duke trying to do something like that -- the point is close to you, right, sort of close to you. But I don't know if you're familiar with that, trying to capture data from a variety of sources, including social networking data, I understand, to know what the impact of change in prescribing patterns are on the larger community.

Look, we all want to do that because then that $15 million is feasible. I mean, the trials that have been floated around here today would not be purchased for $15 million. Maybe the withdrawal one might be, but other than that, they would all cost considerably more than that, in large part because of the costs of data capture, data scrubbing, and data analysis.

To the extent that we can make data a more efficient thing, either through the electronic health records or other mechanisms, is to the extent we can do a lot more trials with your $15 million.

MALE SPEAKER: (Inaudible – off mic.)

DR. THROCKMORTON: The Institutes of Medicine have said, I think, fairly publicly that we're interested. They're trying to sort out, how do you move from a discrete database model for trials to a model that relies on data that are being collected in other formats: electronic health record data, data from social -- how can you use those data to inform efficacy and safety in

more efficient ways.

I think it's something we all look at and say, that's the future of data collection for trialing.

Not seeing anyone standing up, I'm going to please thank everyone that's sitting up here today. And then I've got just a couple of last-minute remarks, and then we'll get people out.

You're welcome to sit down while I go get my remarks, if that's all right. But please thank them for me.

(Applause.)

**Closing Remarks – Douglas Throckmorton**

DR. THROCKMORTON: Thank you for this last discussion. I have the challenging task of trying to summarize what I've heard over the last day and a half.

I'm going to begin with just seem housekeeping. The slides, the references that were submitted to the FDA, all of those things, the transcript, will all be put on the web and made available as soon as possible.

We have to get approvals. Some of the slides have to be made compliant with federal standards and those sorts of things. But we will do all of those things as quickly as we can so that people are able to see the slides that we're given permission to show.

So I want to do two things. First, I'm going to say a little bit about what I heard in the last day and a half. We've talked about that to some extent already this afternoon, and so I won't belabor anything there. Then I'm going to end with some short comments about what I see as the FDA's role in this area, why is it that this is a conference that the FDA and the NIH is holding, as opposed to some other organization?

So first, I'll say again, this meeting is the beginning of a discussion. We need to have this foundation, this discussion of the efficacy, to understand better the course that we need to take as an agency, and I would say, writ large, as a larger group of individuals worrying about the use and abuse of opioid medicines in chronic pain.

The goal is to define the role of opioids in chronic non-cancer pain. I think that's a goal that we all share. We may have different answers to that best use of opioids in chronic non-cancer pain, but I think we can all agree that the present state is not where we want it to be. We want to understand better the efficacy of these products. If necessary, we ought to find ways to better articulate that efficacy to make a positive difference in how they're used.

Thank you to everyone that's commented. Thank you to all of the presenters, the panel discussants, to the people that have come to the microphones. We genuinely are listening to everything that people have said. We are open to all of the opinions that we've heard.

I don't know where this discussion is going to take us. I am not a pain specialist. I'm a kidney doctor by training. I come to this with a genuinely open mind. I see the need for doing better than we're doing at present, and the agency's goal is to understand what "better than at

present" means, what tools we need to use in partnership with you all to make a difference.

So what have I heard in the last couple of days? I think, first, despite large amounts of resources and time and interest and engagement by very smart people, there are many unknowns about the effectiveness of opioid medicines in chronic non-cancer pain.

There are unknowns related to the basic science, the neurobiology of pain, as someone called it; unknowns related to biomarkers that can be used to diagnose or to segregate by treatment the patients that are suffering from pain.

With regards to the clinical data, I think we've had a full discussion. We can agree that we need to know more than we do at present about the effectiveness of opioids in chronic non-cancer pain, identifying the individuals that are going to benefit from them. And I did hear, I would say, discussion, consensus, that there were individuals who benefitted from chronic use of opioids with chronic non-cancer pain.

We also need to have tools to identify the people who will be harmed by the use of opioids in chronic non-cancer pain, and what I heard in this last day and a half is that we need additional tools to help do that as well.

Some people benefit. Some people are harmed. I think that was Jane Ballantyne that said that. Whether it's dose, whether it's some patient characteristic, a genomic marker, a proteomic marker that we can identify, I don't know those answers. But there is a pressing need to be able to have more understanding of those things than we do at present.

What's needed, then? The basic science I think was laid out beautifully in the discussion at the beginning yesterday. Focus on biomarkers for diagnosis and treatment seems particularly necessary for me, especially if we're going to try to do efficient trials to understand better the effectiveness of opioids in chronic non-cancer pain. But I'm certain that there are other fundamental basic science questions that need to

have answers.

We need improved data collection. We talked in this last session about how we collected data and how the kinds of data we have can inform the use of opioids. There's a theme I hear that we need to focus on not just pain but also on function; that is, does someone have pain but they're able to get up and do their activities of daily living?

Penney Cowan did a wonderful job with her card that she showed. That was an aspect that she was asking people with pain that she dealt with. I think it's an important thing for us to keep in mind as well.

We need to find better drugs. Let's be honest. Opioids are imperfect therapeutics for pain. It would be wonderful to identify non-addicting drugs for pain. I know NIDA is here. We're working very hard with them. We've had a very good collaboration, trying to identify those things. It's a crying need, I believe. We're doing anything that we can to help with that.

We need to have improved practice patterns around whatever best practices we identify. I talked about this at the end of this last panel discussion. It's one thing to identify how best people should act, patients and prescribers should act; it's another thing to find ways to effectively get those things taken up and used by individual physicians.

When I was in practice in the middle of Nebraska, I understood it was only me out there making decisions. And we need to find ways to help those physicians, those prescribers of opioids, make the best possible decisions once we understand what the data show us.

So now let me just transition. What's the FDA got in all of this?

First, I'll just say I believe we have an absolutely clear, very important role to play in making opioids safely and effectively used by as many people as is appropriate, as is supported by the evidence. There are at least couple parts of our role.

First is a strictly regulatory one. We have legislative mandates to label medicines for safe and effective use for a defined population. We have legislated mandates to pay attention to safety, legislated mandates to approve and remove from marketing medicines under appropriate circumstances.

Both Bob Rappaport and I take those legislative, those regulatory roles of our job very seriously, and we take them very seriously in this particular area as well.

If the evidence supports changes in labeling, that's something that we will do. It is something that's necessary. The question is not, would we do that? The question is, does the evidence rise to that level? And two, is that the best tool to use to achieve the larger public health good?

I don't know the answer to those questions, but I think it's critical to bear in mind the end that we want, not focus on one tool when there may be other things that could be valuable swallow.

There's another role that the FDA plays, and it's embodied in this meeting. It's one to forward regulatory science. It's a role of forwarding public health outside of our regulatory role.

So Bob saw a convening role for the FDA when he talked to me about having this meeting. He understood that the FDA could sit back. We could sit back and wait for citizen petitions and letters and requests and whatever. Or we could lean forward. We could say, this is something that we have a duty to engage in as a part of our public health mission. That convening role, that role of bringing together people that understand an issue incredibly well and help us see our right way forward is terribly important to us. We take it seriously. We have the meetings very frequently, whenever important scientific issues like this come up.

I'm delighted that the Center was able to support this meeting. I'm delighted that Bob had the vision to try to put that meeting together And I'm particularly delighted that everyone was able

to attend that's been able to help us with that.

Another part of that role as forwarding regulatory science means helping develop new tools. We have a mandate, for instance, to help develop patient-reported outcomes that can be useful not in one trial but across a set of trials. We have a process that we put in place to qualify patient-reported outcomes so that they can be used by a dozen trials, by a trials network, to more efficiently assess the available data, to make the best possible use of the patients that you see, the forward the science more efficiently than we do.

We have an interest in forwarding benefits/ risk assessment. So one of the things that we're doing is setting up a grid. We've set up a semi-quantitative system to assess benefits and risks of products as they're under development and products as they're in the postmarketing setting.

Dr. Rappaport will be applying that benefits/ risks assessment as he thinks his way forward to the right ways for us to deal with the issues that have been presented the last day and a

half. It's essential that we keep both of those things in mind as we think about our regulatory role, what are the benefits of the action, what are the risks of the action, and how much uncertainty do we have around what will happen if we take that action? What risks, what potential down sides, would there be?

Then I guess the last thing -- and this is just something that's come out in the discussion -- FDA is very interested in meta-analytic techniques. We've heard over the last day and a half a variety of guidelines and a variety of Cochrane reports and various analytics, putting together sets of data and coming up with conclusions.

Several of the speakers commented on how, somehow, two groups could look at the same data and come up with fundamentally different conclusions. That sends a mixed message. When that happens, it sends a mixed message to the practicing community that we're not exactly certain what the right way forward is.

One way to address that is to have in mind, in clear mind, what the best possible ways to use meta-analytic techniques are, something that the FDA sees, something that I hope this group continues to work with as well.

So, fundamentally, regulatory science and advancing regulatory science, from my perspective, is important because it supports the regulatory activities that the FDA takes, that we have to take, and it helps enable more efficient medical products development, whether it's new drugs or it's new analgesics that have lower risks of abuse and misuse; or it's better uses of existing products, whether it's abuse-deterrent formulations or the like.

My last comment, then, is to pull away from the FDA. I am in the FDA. I understand my job within the FDA, the role that the FDA plays within this issue. I also understand we are one part of a very large group of people, a large group of organizations and institutions that have a role to play here.

FDA can't solve this alone. Academics can't solve this alone. Patient groups can't solve this alone. We need to all of us keep in mind what our individual responsibilities are, find the most efficient way to change the behaviors rather than look for a single effect or model to try to make things happen. We need to be doing a great many things and not one single thing and trying to identify that single thing.

I very much appreciate all of the comments that have been made over the last day and a half. I'm looking forward to continuing to talk with Bob and the internal group to decide where the next steps are. Whether that's additional meetings, exactly what that is, I can't say. But we genuinely appreciate your input.

Thank you so much to everyone that commented. And thank you for staying with us here until 4:30 in the afternoon. Appreciate it.

(Applause.)

(Whereupon, at 4:43 p.m., the meeting was concluded.)