ACTTION - IMMPACT XXI - OPIOID SPARING IN PATIENTS WITH ACUTE AND CHRONIC PAIN

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ACTTION

INITIATIVE ON METHODS, MEASUREMENT, AND PAIN ASSESSMENT IN CLINICAL TRIALS

IMMPACT-XXI

Research Design Recommendations for Clinical Trials of Opioid Sparing in Patients with Acute and Chronic Pain

Thursday, July 26, 2018
8:15 a.m. to 5:32 p.m.

The Westin City Center
Washington, DC

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)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:15 a.m.)

Welcome and Introductions

DR. TURK: Good morning. I want to thank you all for being here for this particular meeting. This is the 21st IMMPACT meeting. For those that have been around that long, they've been to some of those. Some of us had black hair when they started; the rest of us look like me.

(Laughter.)

My name is Dennis Turk. I'm from the University of Washington in Seattle, and I've been involved with Bob Dworkin with the IMMPACT meeting since 2002, I believe, so we've been here for a while. I want to thank the sponsors who are supporting this particular meeting. That includes the public-private partnership from ACTTION, which you'll get used to these acronyms. I'll just tell you what they are, ACTTION and IMMPACT.

IMMPACT is the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. It originally started out as an entity in

itself. It subsequently was folded into the ACTTION initiative. ACTTION stands for -- and Bob, you'll have to correct me because I always get this mixed up -- stands for Analgesic, Aesthetic, Addiction, Clinical Trials, Translations, Innovations, Opportunities, and Networks.

You may be wondering why aren't there three A's there. Historically, it started out with one A; it was just analgesic. And this is a public-private partnership between the University of Rochester and the U.S. Food and Drug Administration. A public-private partnership means we work together, but it should not assume -- no one should assume that anything that we have published or that we've put out is the result of a governmental policy or the FDA policy. It is just the discussions, conversations, agreements that we have among those people in the group, who then will create manuscripts.

Of you're familiar at all with IMMPACT, you'll know that there are IMMPACT manuscripts. By the way, ACTTION.org or IMMPACT.org, you can go see

all the background papers and manuscripts that we've developed over time.

I don't see Sharon Hertz or Allison, and I can't see all that far back. But those are the people from the FDA who have worked heavily with us, and I want to thank them for all of the assistance they've given us over the years since ACTTION began, which was 2012. So IMMPACT started 2002, and then it moved forward.

What we're going to try to do today is take up a very interesting issue, task, a timely one, which is related to the concept of opioid sparing and how its relevance and importance are going to be handled within clinical trials of acute pain and chronic pain. So we're going to be a little schizophrenia because we'll be going back and forth between acute and chronic pain.

But the goal, however, is to talk about, first of all, what do we mean by opioid sparing. Why is it important in both acute and chronic trials? How do you measure this? Do we consider objective measures, subjective measures, both of

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those types of measures? How do we use those? What's a clinically important or a meaningful effect of any type of treatment? Is it from the patient's perspective? Is it from the actual provider's perspective? Is it from the actual use of the drug?

The way that we formatted this meeting is to address those types of topics, and you'll hear much more detail about those. If you look at the agenda, you can see all the things that will be covered. We purposely intentionally structure all IMMPACT meetings -- and this one in particular -- that we have lots of breakout time, coffee breaks, lots of lunch times, dinner times; the idea being that what happens in this session, these meetings, that's just part of it, maybe even the smallest part of what's going to come out of this, because we're hoping that that leads you to raise questions, to have more discussions among yourselves, and to then bring them up to the group.

We've also structured that by the end of the day tomorrow -- and we won't let you leave until we

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do this -- we have to come up with some recommendations. So if any one of you here was going to plan a clinical trial next week, you would have some suggestions, some recommendations, and some considerations for you. Admittedly, we're all going to say, you need more data, you need more evidence, et cetera. And that's true, but if you're writing your grant on Monday, you can't wait for all those data. So what you have to do is go with what's the best information you have at this particular point in time.

So we will come up with some recommendations. Everyone in this room is invited to be an author of those manuscripts. And what that means is we have a person who is what we call a rapporteur.

Jen, are you -- where is Jen? I can't see her. Would you stand up just so people can see you? She's an important person because Jen is going to be taking notes and minutes. And if she hasn't understood something you've said, she's going to come to you and try to make sure for

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clarification, because she's going to make the first draft.

Now, we totally understand that when we leave tomorrow, or when you leave tomorrow, that this isn't a final product; that we still have issues that haven't been resolved to be discussed. What Jen will do is draft up a manuscript. The steering committee will review it and add comments to it. It will then go to all of you, asking you, begging you to look at this, to make comments on that, make suggestions, things we left out, things that were unclear, things that we didn't define appropriately.

We'll give you a reasonable time, and by reasonable -- as you look around the room, you see the number of people here, and you can understand what fun that is trying to get 50-plus people to agree. Now, if you choose not to or if your agency that you are representing won't permit you, that's fine. We understand that. But if you do want to, then we strongly urge you to make sure you follow the deadlines, and suggestions are going to be

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given.

Having done this a while back, let me tell you that someone sending an email saying, "Great job" is not real helpful, or "There's some grammatical errors or typos," that's not helpful. So what we really need from you is not just those kind of comments, which are fine if you catch them because surely there will be some of those. But if there are certain points that you think we really need to make, or we missed, or we need clarification, you think should be expanded, need to be shortened --

We've initially envisioned this as being a single manuscript. However, it may be the case that that's too much to try to cover in one paper, so it may end up there will a separate one on acute pain and a separate one on chronic pain because of some of the uniqueness's of those. We'll see if it works that way. But those will be circulated. It takes usually 3, 4, 5, 6 months before you'll see something, so don't think we've forgotten you.

All of the presentations, all of the

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discussions, everything that goes on in this room will be transcribed, so it's essential that when you raise your hand, or ask a question, or start talking, that you say your name and where you're from because the person who's transcribing this is not going to be able to determine when we have multiple people speaking and to assume that she or he -- I'm not sure who's transcribing this -- is going to be able to be aware of all that. So it's really important that you do it.

The microphones that you have in front of you, you have to push the button for them to come on. A red light will go on. They're set up so after a certain number of people on there, it won't let anybody else come on until those are freed up. If you happen to push the button and it starts blinking your red light, that means hold off; you can't get in right now. Do it the next time. When you have spoken and asked your question, whatever you want to say, turn it off so that we can get people to do that.

So that's just the logistics about the

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microphones and transcript. And all of the slides, we will ask all the speakers, with their permission, to have their slides put on the website for IMMPACT.org and ACTTION.org so that the many people who wanted to be here or couldn't be here -- and we've intentionally made these -- we used to say small meetings, but it's not getting small anymore. But the intention was to try to make these nimble, efficient, and encourage conversations, which means that many people who would like to be here or would have something to contribute, won't be here. Unfortunately, we just can't do it that way.

So therefore, we try to get around that by, number one, we put information on the website about the meeting, who was here and what the topics were. We'll put all the slides, as many as possible that we get permission for. And if you're one of the speakers and any of your slides are proprietary, by all means, you can delete those and say these are fine but delete slide 3, or 5, or whatever it happens to be. Those will be on the website

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available, so the people who couldn't be here would be able to see those and understand what we've been doing.

So let me put up the first slide of just housekeeping details. Here we go. I can't even read this, so I'm going to step over here.

Sign the registration if you haven't signed in, and that means sign in and out both days so we know who was here. Cell phones, silence them. You've heard that enough times, if you go into a movie or a meeting. Please do that. It's really distracting to presenters. I mentioned about the -- they're not voice activated, so disregard the microphones. Go by what I told you. You have to push the button. They're not voice activated, too many people. And only a certain number can be lit up at one time. And if you try to push the button when there's too many on, you just get a blinking red light. Just wait for your question.

Meeting is being recorded as well as being transcribed. All this information will be made available, so don't say anything that you don't

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want people to know. These microphones are indeed sensitive, so if you're whispering to your friend about where you're going to dinner tonight, we're all going to hear it. Now, if you want us to know where you're going, that's fine, but if not, then try not to make any noise when the microphones are on near you.

The internet code, which is essential for many people, is impact2018, so if you trying to get on the internet while you're. Restrooms are located outside this room and to the right. Valorie Thompson, who most of you should have met, and Julie are out there at that desk. If you get lost, they can point you to the right direction. Any questions you have about the logistics, about your stay, your room, taxis to someplace, Valorie and Julie can answer that for you. They've done this for many, many years for us, so they're quite capable of doing it, quite good at doing it.

Lunch will be in the same room we had breakfast, in Monticello East. Dinner will be -- son of a gun -- same room. So it's a

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reliability check to see if you've learned anything, where to go. Check out is 12:00 tomorrow. There's luggage either at the bell stand or we'll be able to store it for you here.

If you need any assistance, as I said, talk to Valorie or Julie, and they're very helpful. And most of you should have had communications with them, at least email, and now you can go say hello to them. They're sitting out there, so I won't --

Valorie? Come in and let me show people in case they don't know who you are, and to thank you.

Valorie Thompson, the young woman with the blonde hair. Valorie is the organizer for this. She is the person that we couldn't do anything or get this set up without her. So thank her for that, and for all the things she's going to do.

(Applause.)

DR. TURK: Thank you.

Any questions that you have about the logistics, about what our intention is? And remember, we're going to herd the cats, so tomorrow you cannot leave -- we will lock the doors -- until

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we have a preparation for the manuscript that Jen is able to do. So my flight is late, so I'm quite happy to stay a lot later than some of you. We strongly encourage you to stay through the entire meeting because toward the end is when we sort of come with recommendations, and that's really the critical point for you to be here. So if at all possible, and we know certain times that can't happen.

Any questions you have for me? Bob Dworkin is sitting over there, my perpetrator, co-perpetrator. Jen Gewandter, you've seen; Shannon Smith. Rob Edwards, raise your hand and Kushang is not here. Those are the people from ACTTION who have been involved with ACTTION and the development.

So thanks to all of them for the work. You'll be hearing more from Shannon and from Gen as the meeting goes on. Rob, I, we have you moderating somebody yet. Okay. So you'll be hearing more from Shannon and from Jen as the meeting goes on.

Rob, we have you moderating, so you'll be

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hearing more from him. So I've got through the thank yous.

Any questions about the logistics or about what we're about and what we hope to accomplish with this meeting, and what your responsibilities are?

(No response.)

DR. TURK: That's too easy. No questions?

Bob Jamison, nothing to comment? All right.

So what I want to do now is I'm going to turn this over to the moderator for this morning session. Kurt Kroenke will be introducing the speakers for the morning. He will also be the chair of the question and answer period. John Farrar was supposed to be doing this with him. John had trouble with his flights.

Is he going to get in? So he'll be in later. He may be here in time for some things. He's not here.

Kurt, if you want to come up? Some of you may know Dr. Kurk Kroenke, at least most of you if not everybody knows Kurt Kroenke because he's been

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around for a long time, as I have. Kurt is a professor of medicine and research scientist at the Indiana University School of Medicine, and he's also from the VA in Indianapolis. So Kurt's going to be the moderator for this session. Any questions you have along the way, by all means, at break time if you have questions for Bob, myself, Jen, Shannon when you're here, and Rob, we'll be happy to answer them.

So, Kurt, I'll give you the podium.

DR. KROENKE: Yes. So we have a series of 30-minute presentations this morning I think by five speakers. There will be a 30-minute break I think after the third one. So it'll be a tight timeline. My only job this morning is to introduce people and make sure people end on time. So if someone's getting close, I'll start waving, and if they're starting to go over, I'll stand, so we can make sure everybody gets -- which means if the speaker ends shortly before the end of the 30 minutes, there may be time for a few questions. We won't have 15 minutes of discussions, clarifying

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questions. But there's a generous discussion session over the 2-hour working lunch. So that's where we hope there's going to be a lot of questions triggered by the morning speakers, and we'll be up here in a panel.

The first speaker is going to be Eric Strain, who's professor of psychiatry and behavioral sciences, director at Center of Substance Abuse and Treatment; executive vice chair for the Department of Psychiatry and Behavioral Sciences and also directs the behavioral pharmacology research unit at Johns Hopkins. So I'll have Eric come forward. And he's going to be speaking on what do we mean by opioid sparing and its potential benefits.

Presentation - Eric Strain

DR. STRAIN: Great. Thank you. And thanks for inviting me here today to ACTTION for this.

These are my disclosures for various activities over the past year. I want to begin by saying I'm a fish out of water on much of this topic. I'm an addiction psychiatrist, and I don't

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typically prescribe opioids for pain. Certainly, opioids for the treatment of opiate use disorder is something I'm familiar with, very familiar with, from over the years. I appreciate being invited here today to talk about. And it's been very intriguing and interesting to sort of contemplate the topic area and see what I can perhaps shed light on it about.

Over the next 30 minutes, I'm going to talk about what I think we mean by opioid sparing, as I understand it; why do we care about opioid sparing; does opioid sparing matter; and then wrap up with some final thoughts. So let me jump into it and talk about what do we mean by opioid sparing.

I think we mean strategies that accomplish one of the following. And I realize I'm perhaps preaching to the choir here or trying to deliver a message. Maybe I'm preaching to a group of ministers here who already know the message I'm trying to convey. I think we mean either a decrease in the acute dose of opiate that's taken or a decrease in the total number of doses of

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opioid taken; a decrease in some aspect of the opioid effect, for example, a side effect; or not requiring the use of an opioid.

I want to over the next few minutes kind of peel these ideas away and think them through with you. And to also think about -- which I think is one of my tasks -- does this matter from an individual in a societal perspective, which is something that I found myself coming back to as I was putting this talk together.

Underlying this is the assumption that there's at least no change in outcome with respect to the target clinical measure, typically analgesia. I think that's what the idea is here, that okay, can we give people opioids, not have a decrement an analgesic effect, but have a decrement in something else related to the opioid exposure? At least it strikes me that that's what the striving is for.

So why do we care about opioid sparing? I think this is where I really kind of start to dig into it and think about this. In case anybody has

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been living under a rock for the last year or two, we have what's variously called in my field of addiction either abuse, misuse, addiction, dependence, or a use disorder problem. Actually, if you're not aware of it, there's considerable controversy about virtually all of these terms, in some cases whether they are politically correct to use, such as addiction dependence, which was used in DSM-4, the psychiatric nomenclature, and has been dropped because of the difficulties in understanding physical dependence from syndromic dependence; abuse and misuse is an overused term; and what is now the current term, which you're probably familiar with, which is opioid-use disorder or OUD, what has been now promulgated in DSM-5.

If you haven't -- I'd just be curious, a show of hands. Has anybody reading this book?

(Show of hands.)

DR. STRAIN: Okay. Great. This is Dreamland. It's a good 200-page book that lasts 300 pages.

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(Laughter.)
DR. STRAIN: If you've read it, he sort of is repetitive. But at the same time, if you're interested in this topic and really understanding -- and having grown up in Ohio, which is part of the area that he talks about, having seen some of these towns that have been devastated by the opioid epidemic, this really does give you a real sense of what it's been like over the last 10, 15 years, and I highly recommend it, especially on long plane rides.
So why do we care about opioid sparing? Well, we have this problem, as I mentioned, and the underlying assumption is that decreasing exposure to prescription opioids will decrease the risk of developing problematic opiate use. Right? That's what we're hoping for I think. And we're looking for both an individual and a societal benefit, or at least that was I think what the organizers asked me to consider as I was contemplating this topic.
How bad is the problem of opioid abuse in the U.S.? I want to take a few minutes and just

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make sure -- I suspect, again, that all of you are familiar with this, but to just make sure that we're all on the same page and to really bring this home. And I think this is part of what I'm being asked to do here.
This is opioid prescriptions dispensed in the U.S., and I'm going to walk you through this slide in case you haven't seen it before. This is IMS health data that's come out. And what we have on the Y-axis is the prescriptions in millions prescribed, and then we have all opioids, hydrocodone and oxycodone here, the blue, the red, the green. Along the X-axis, then we have years, and this is through 2013.
Of course, what's striking about this is that there's been a steady increase in opioid prescriptions that appears to have peaked in 2011 in this country at 219 million, which is of course a remarkable number, and that's almost a threefold increase from 1991. And I think we're all familiar with now this song about how this came about and how problematic it is. One of the questions is,

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are we starting to see some decrease since that peak in 2011? There's some evidence that it's starting to taper down.
I'm going to come back to this, but one of the things I think we have to consider is whether that's good or bad. There's this underlying assumption that, well, gee, that's really good. We're decreasing the prescribing of opioids. I think it's a more nuanced answer than that. I think that comes up and then raises questions of are we undertreating pain; are we shifting opiate use to other types of opioids? So just because we're decreasing prescription opioid use does not necessarily mean that we're solving the problem as it were.
Another problem with respect to opioid use is overdose deaths from the use of opioids. Again, I think that people are familiar with this, but just to familiarize you with these data -- and I'll again walk you through the slide. This is a figure that just came out recently on drugs involved in overdose deaths in the U.s. between the years 2000

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and 2016, and there's the title.
What we have is we have -- just to make sure it hits home in case you don't -- because it's not clear in the actual body of the figure. We had 64,000 drug overdose deaths in 2016 in the U.S., which is really remarkable. And you've heard all about how that is relative to auto accidents and various other ways that people have hurt themselves.
Along the Y-axis here, we have the number of deaths. What we see here is -- let me back up. I'm going to walk you through -- there are essentially three trends that we're seeing here, and I'm going to walk you through the three trends that have been identified with this figure.
The first trend is a slow, steady rise in prescription opioid overdose deaths. This started around the year 2000, and you can see it climbing up there. It's characterized as natural and semi-synthetic opioids, which in 2016, there were a little over 14,000 deaths from prescription opioids. So that was the first trend that we saw.

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The second trend began around 2010. This is -- and it's got a steeper slope -- heroin overdose deaths, which now have exceeded in 2016, prescription opioid overdose deaths, by about a thousand, almost exactly a thousand cases. We had this first slow, steady increase prescription opioids, then we started to see heroin overdose deaths.

Now, what we see starting in 2014 is this very sharp rise, astronomical rise, in essentially what are fentanyl overdose deaths or synthetic opioids other than methadone, which have exceeded both heroin and prescription opiate overdose deaths, a little over 20,000 in 2016.

I want to show this slide, which you're probably familiar with as well. This is a CDC slide. And this is what I would have showed you if we were talking two years ago. Probably I wouldn't have paid a whole lot of attention to fentanyl overdose deaths, which were down there. Then we were looking at the heroin, that blue line there. And really, fentanyl, tramadol, those deaths were

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not showing up on the radar screen the way they suddenly have come about now. It's interesting to see.

This translates to a change in the U.s. s death rate. This is all-cause mortality ages 45 to 54 for various demographic groups in developed countries. I will again walk you through this. This is deaths per 10,000 on the Y-axis. Basically, what we see is different countries here, and this is U.S. white, non-Hispanics. And you can see that red line is actually trending upwards, which is remarkable. So white overdose deaths are really accounting for that, and there you see it there.

That compares to a variety of comparable countries. The green is France, the blue is Germany, just going down. The next one is U.S. Hispanics. The next is the UK, then Canada, Australia, and Sweden. So comparable countries all trending downwards in this country for U.S. whites, it's been steady. And that's U.S. Hispanics. So it's very much been -- and as noted in Dreamland,

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it's been a phenomenon that's been seen particularly in U.S. white males in this country, and there are the Hispanics.

Now, I just want to make a point because not in that slide, but something that's been brought up just recently, these are, again, data on drug poisonings by race and age and sex in the U.S. What's been pointed out here is for non-Hispanic blacks, the rate of increase in the last year has gone up greater than other demographic groups.

So there's been some concern that because culturally and socially there's been a lot of attention on, oh, this is a phenomenon of Midwest whites in small towns, West Virginia, Kentucky, Ohio, sort of that, that's the place where this is a problem. And there's been some recognition or some statements, I think appropriately, saying we can't make this just about whites, middle-class young white males.

I also want to make this point. We're very focused right now on opioid use and opioid overdoses, but we don't have an opioid problem. We

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have a substance-use problem in this country, and we're playing Whac-A-Mole so long as we focus on one drug type or drug class. And I think that's really important to stress. So I think probably everybody in this room knows that there's $500 million of NIH money for the HEAL Initiative; we're going to take care of opioids. But we have this tendency to focus for a few years on a drug class or a drug problem, and then something else comes up because we become maniacally focused on just one drug problem.

I'd point out to you -- this going back to the slide -- buried in this slide is cocaine overdose deaths, which are trending up. Right? So we're so focused on opioids, we haven't really -- I'm being global and generalizing, but we're sort of forgetting about cocaine and stimulants. People who deal drugs are not going to simply go out of business if we expand treatment capacity for opioids and get everybody in treatment. They're simply going to shift their product to some stimulant or some other drug class

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and move in that direction.
Perhaps our biggest hope -- and I probably shouldn't say this because it's being recorded -- is that they'll go into legal cannabis rather than an illicit drug because that might be a way to address this.
(Laughter.)
DR. STRAIN: So let me talk about where do people get opioids, and especially prescription opioids. This actually varies as a function of whether we have problematic use of prescription opioids or not, the person. These are some data that was published by NIDA. Wilson Compton did this in the Annals of Internal Medicine last year. He used the National Survey on Drug Use and Health Data. It's a national database of data that is published annually a on this, and I'll just quickly walk you through this slide and these data.
They stratified into two groups from adults reporting misuse without a use disorder, so somebody who's got lower level use of a drug, and then adults reporting use disorder, so somebody

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who's got problematic use of opioids. We've got two groups here, and where do they get their sources?
Well, if you don't have a use disorder -- so if you're using on the weekends, sporadically, early in the use, you're misusing but have not become problematic -- you tend to get it free from friends or relatives. So these are people who are getting it from their moms, their grandmoms, or picking it up out of the medicine cabinets or things like that. There's a twofold difference; as opposed to people with a use disorder who less likely are going to get it from a friend or relative.
If you have a use disorder, you're more likely to buy it from a friend or relative -- that's more common -- or you're going to buy it from a drug dealer or a stranger. So as you worsen in the severity of your use, you tend to migrate out of getting it for free into getting it from other sources, typically purchasing it.
Let me summarize this part of my talk with a

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couple of slides. Increased exposure to opioids has resulted in more problematic use. I do want to say -- and I thought about going into this in some detail and didn't -- why people use opioids is complicated, and just getting opioids is not the reason people misuse them. Plenty of people get opioids and don't develop misuse or some of them may take an opioid and say, gee, I really like how it feels; I'm not going to take it anymore.
Exposure has been related in part to increase prescribing of prescription opioids and also to increase overdose deaths, as we've talked about. Some proportion of people exposed to an opioid go on to develop problematic use of it; although I don't think we really know what that is. I don't think we can say -- we've got some data and can say that. It's going to vary, though, depending upon which data set you look at and how you interpret those data.
But even for those who don't directly develop a problem after exposure, the availability of opioids may result in diversion to others who

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then developed misuse of opioids. So we certainly see that where people who are getting prescriptions may not develop a problem, but because they've got availability of opioids, they're passing them on to others.
So does opioid sparing matter? I'm on the home stretch here. I think if sparing means no exposure to an opioid, then it's likely that sparing matters. We decrease the denominator under the circumstances of what is probably some relatively stable ratio of people who run the risk of developing an opiate use disorder, so we eventually decrease the number with problematic use. So if we say -- and I'm just making it up -- 15 percent of people who get exposed to an opioid are at risk for developing opioid-use disorder, if we can just decrease the denominator, then we'll decrease the number of total people who have that.
On the other hand, if we decrease the amount of exposure, the number of prescriptions, the amount that's provided in a prescription, the dose

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within a dose, the dose within a prescription, but not the experience of being exposed to an opioid, then this probably gets more complicated I think because I've thought about it.

So as something of an outsider or fish out of water, let me take you through what I think. And you guys probably have thought about this a lot more than I have. So if we decrease the amount of exposure, first of all, I think we have to recognize the exposure to an opioid induces some immediate changes. We know about acute physical dependence, for example, that there's some physiologic effect that occurs with just a single dose of an opioid in naive humans and animals as well, so maybe it doesn't really matter for the individual.

It's interesting here because clinical experience of the first dose by people who go on to develop an opiate use disorder is they like it from the start. Not everybody, but a lot of them report that. If you read anecdotal reports of people of the first time they ever took heroin or things like

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that, what they say is that when they took an opioid, they felt nauseous. They maybe threw up, first time in heroin or something like that. And then they get this warm feeling, and they really felt good, and they really liked it.

It's interesting that way. So it could be that there are people where it doesn't matter if you say, well, we're only going to give somebody a week's worth of opioids rather than a month's worth because it may be within that first week they're going to have that experience that says this is God's breath on me or things like that. So it may not matter there.

Second, if we decrease the amount, certainly there's more typical physical dependence with the repeated chronic exposure, depending upon what I'd call the three D's: the drug, the dose, and the number of days that the person gets it. So we decrease the risk of physical dependence if we decrease the total amount of exposure. But then physical dependence isn't necessarily problematic use, although physical dependence can run in

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parallel with problematic use. And certainly it becomes more complicated for people who like opioids when they become physically dependent upon them under chronic exposure.

Then third, more doses out there runs the risk of more potential for diversion and misuse. Here I would note that decreasing availability of prescription opioids, which appears to be occurring, is just shifting us to having people now use heroin and fentanyl. So we've got unintended consequences. We may be seeing increased opiate overdose deaths and increased mortality because we've shut off prescription opioids, and people now rather than taking a very quantifiable amount of an opioid are using an unquantifiable amount of opioid that they get from a dealer.

However, there may be a long-term value to decreasing the doses out there, so that may have long-term effects because we decrease the amount of total exposure, we decrease the number of people entering the pipeline with an opiate use disorder. But in the shorter term, we actually may be

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increasing the individual and societal costs, such as deaths, because we're clamping down on prescription opiate use, which would be part of opioid sparing.

Opioid sparing could also have other repercussions. Alternative treatments could be more expensive to the healthcare system. As I was saying to Bob or Dennis, I'm on service this month actually, and working with managed care is just lousy. If you're in the clinical trenches, you know. They're not looking for something that's going to be a more expensive if you offer a strategy that says, well, I can give somebody something that will decrease their the risk of opioid exposure.

Use of another substance could have more downstream problems either at the individual level or the societal level. I took out, but I had some slides when you Google opioid sparing, two of the top hits are related to cannabis. Everybody now is sort of on the cannabis bandwagon. And I could talk for hours about cannabis use because we're on

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a grand social experiment there that's not data driven, not that you might detect my personal biases on that.

(Laughter.)

DR. STRAIN: But we've got this experiment that we're engaged in, and we now have a really big industry, and Canada is going to have an even bigger one, that is pushing this forward, this agenda, that the solution to the opioid problem is to increase availability of cannabis. And we really don't know what the downstream effects are going to be of cannabis.

Again, if the ratio is the same but the exposure is increased, the denominator increases, the numerator increases, and people do develop cannabis-use disorder. There's NSDUH data that suggests about 15 to 17 percent of people exposed to cannabis develop a cannabis problem. And then individual efficacy may be lower as we think about opioid sparing and how that works.

So the bottom line, opioid sparing can have value for the individual prescribed and for society

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I think. Certainly, I'm for it. However, it's important to note that as we decrease prescription opiate abuse and exposure, we're seeing a backfilling with illicit opioid use, for example, fentanyl And sparing by itself won't solve the opioid problem, and it may be actually producing more societal pain and individual suffering as we go down this path.

Final thoughts, the value of opioid sparing likely depends upon the approach used to spare the opioid. The drive to spare opioid use is good, it's reasonable. It's hard to argue against it, especially to lay audiences. And likely, it could decrease the further development of opioids.

(Loud audio sound.)

DR. STRAIN: My time's up?

(Laughter.)

DR. STRAIN: I have that soporific effect.

And like you can decrease further the development of opioid-use problems, we have passed the prescription opioid phase of the crisis. Overdose deaths are fentanyl, heroin, and

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prescription opioids in rank order. And finally -- and I keep trying to figure out how to say this, and I'll figure it out eventually. But the problem did not develop overnight, and the solution will not be equally quick as a fix, despite desires to do so and good intentions.

I think that's what worries me the most is we're going to give $500 million to NIH, and NIH should solve this problem in the next 14 to 18 months. I'm looking at Ewan, and Dave, and Kurt, you guys. And that's not going to be the case. It took us years to get here, and it's going to take us years to get out of this problem. And we are going to now have this larger population with opiate use disorder that we've got to accommodate in ways in terms of treatment capacity and healthcare needs going forward.

So with that, I thank you, and I'm done.

(Applause.)

DR. KROENKE: We have time for a few questions. [Inaudible - off mic.]

DR. RATHMELL: Jim Rathmell from Brigham

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Women. You speak with such wisdom of being in front of these people who are experiencing this in reality. Can you speak to someone who's been on chronic opioids for treatment of chronic pain for a very long period of time, now faced with practitioners who will no longer do that, from both the patient's perspective, the primary care doctor's perspective and someone like yourself who might all see the same patient over the course of a few weeks or months?

DR. STRAIN: One, I think the idea that this person who's been on a chronic dose of hydromorphone or morphine, MS Contin or something for chronic low back pain for years, has done well, the idea that this person now needs -- I've got a psychiatric patient I just saw the other day who's got bipolar II disorder, but he's been on a chronic dose of oxycodone for years for low back pain, a stable dose. He gets it from an internist on our campus.

I think it's nuts to be counseling him to come off his pain. He's got terrible both knee

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pain and low back pain. And he's been stable. He doesn't abuse it. The prescription drug monitoring program doesn't show any evidence of that. His prescriptions are stable that way.

DR. RATHMELL: Now they're on 10 times the CDC recommended doses. And it's the same patient. They've been stable. They've been following all the rules. There's no evidence of -- what do you do with that patient when the practitioner is saying I'm getting DEA visits and the like? The same exact scenario, though.

DR. STRAIN: Well, I'm not sure, but I would document carefully. That's one of my mantras that I fall back on. Make sure that there's been good documentation about what's been going on in the treatment, why the treatment is necessary, and things like that.

Again, I think the prescription drug monitoring programs work to our advantage in that respect because I've got patients I prescribe benzos to certainly, and they're beautiful, the PDMP, at least in Maryland, it shows me every 30

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days, or thereabouts, 28 to 32 days, the prescription being filled. And I use that to my advantage in terms of the justification for ongoing use of it. But beyond that I think, I don't know if I've got any wisdom. I have low wisdom.

DR. RATHMELL: One last question --

DR. KROENKE: [Inaudible - off mic] one question from Brett. I saw a lot of other hands, which means we're going to have a really good discussion at the end. So, Brett, one question.

DR. STACEY: This is less of a question and more of a comment, to fess up. I'm Brett Stacey. I'm from the University of Washington. I've known Dennis Turk for a long time.

(Laughter.)

DR. STACEY: That's okay if he talks over me.

DR. STRAIN: Dennis is dementing.

DR. STACEY: If we go back to the start of the careers of almost everybody in this room, we were focused on pain treatment, not on substance abuse, and very few people started off as

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substance-abuse treaters. And I think part of your talk was excellent, but it was on part of the issue. Part of the issue is the opioid crisis. That's only a small part of the issue.

The other issue is that there are dose-related adverse effects for chronic pain patients: depression, endocrine effects, increased likelihood of getting a driving problem, on and on and on, which are separate from the opioid crisis.

If all we do is focus on the opioid crisis, we aren't being pain people. We are paying people as well. We want to treat pain, and we want to look at the appropriate role in opioid dosing. So there are a lot of other adverse effects of opioids besides death and besides opioid-use disorder. And that is a much more nuanced and problematic discussion as a couple of people in here can testify to a breakfast discussion about this. So we need to make sure we explore that, too, when we talk about opioid sparing and opioid reduction.

DR. STRAIN: Great point. Thank you.

DR. KLUETZ: I saw hands up, so I don't

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think I'll have to talk much during the moderating session at lunch.

Our next speaker is, Dr. Tong Joo Gan, professor and chairman, department of anesthesia at Stony Brook School of Medicine in New York. He's going to be talking about opiate sparing clinical trial objectives and outcomes for acute pain.

Presentation - Tong Joo Gan

DR. GAN: Good morning. Thank you for the introduction. My name is TJ Gan. I am, as he said, at Stony Brook. I went there four years ago, and before I was at Duke University for over 20 years. I'm asked to address on this topic, on opioid-sparing clinical trial objectives and outcomes focused on acute pain. Dr. Katz that follows me later is going to talk about chronic pain.

Why am I interested in this topic? Really, I think for two reasons. One is that I'm a clinical anesthesiologist. I see patients, many in the acute pain setting, and we use a lot of opioids, naturally, during surgery, after surgery

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to control their pain. As Dr. Stacey was saying, we are pain doctors, and we try to manage pain, but at the same time, we see a lot of opiate related side effects.

From my second perspective, as a clinical trialist, I've been involved in many of the analgesics coming on the market over the last 20 years, and many of them don't come to the market over the last 20 years, and trying to design studies that would show the value of not only analgesia, but also, on the other hand, the side effects profile. As you know, a drug is on the efficacy and side effects profile, and how can we measure that, and how do we make it as a -- from the patient perspective, how valuable is that?

So those are the two aspects that I constantly think about, how can we better manage pain and also manage opiate side effects. And secondly, how do we demonstrate the value of a drug?

So let's define the outline that I'm going to talk about. First of all, again, I'll just

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introduce some of the opiate adverse events that many of you in the audience are probably very familiar with, so I could probably go fairly quickly, and then talk about the opioid sparing in the context of clinical practice today.

As you know, over the last 20 years or so, our pain management is sort of going in circles. At one point, we got pain with vital signs. Everyone should have no pain. The first thing you ask when a patient shows up in clinic is whether you have pain or not; it doesn't matter what their complaints are. Then, too, when we are embracing multimodal analgesia, using them as non-opioids. And more recently in a perioperative setting, with enhanced recovery, a concept that is starting to be embraced. And this is a multimodal, multi-specialty approach to take care of perioperative patients.

Within that, we are obviously focusing on managing pain, and I want to share some of the thoughts about how does one assess opiate sparing and how does one assess opioid side effects within

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the context of enhanced recovery, which is really a part of clinical practice today, and then briefly talk about assessment of opioid related adverse events, the objective, some of the objective outcomes and some of the more subjective patient-reported outcomes.

Now again, this is a study that Jeff Apfelbaum and I undertook a number of years ago, basically just simply asking patients about their pain experience after surgery. I didn't show you the slide on the incidence of pain, but the gist of it is that many of our patients have pain postoperatively. Over 50 percent of our patients said their pain was either severe or extreme at some point after surgery, within 6 weeks after their surgery.

When we ask them, tell us a little bit about your side effects that you experienced, we didn't mention anything about opioids, but just tell us about some of the things that you experienced that you did not like to experience. And this is the list of symptoms from the patients who said at some

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point after surgery, these are some of the side effects.

Now, if you go down the list, you can see that almost everyone could potentially be related to opioid side effects: drowsiness, nausea, constipation, dizziness, vomiting, you name it. So clearly, opioid side effects are very, very common.

We all know that opioids that unrelieve pain post-surgically can have problems from inadequate or increased sympathetic tone resulting in increased oxygen demands, and in patients who are already teetering at a border can potentially develop ischemic heart disease and myocardial infarction. We also know that if they can't breathe deeply, they potentially can get chest infection resulting in pneumonia, and also obviously they can't have a good sleep, especially after surgery, if they have pain. So there are many reasons to want to treat pain.

We also heard that now with the opioid crisis -- and I'm not going to talk more about that but just to say recently there were studies

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suggesting that in fact 1 in 10 patients reported become addicted to opioids following surgery. These are situations where I'm sure many of you are familiar with. You had a minor procedure, and you are being sent home with 60, 90 pills of Percocet, Vicodin, and most of the people take about 3 or 5, and they kept the rest in their medicine cabinet to be helped by friends and relatives who come and visit. So clearly, it is a problem, and it is something that we are solving.

The other interesting thing about opioids and side effects is that we sometimes don't realize how much impact it has on the cost of healthcare delivery on the length of hospital stay. This is a study that we published a few years ago using the PRIMIER database, just looking at the patient discharge with an opiate related adverse events and compare to those patients without an opiate related adverse events. And as you can see, those who had opiate adverse events not only had an increased length of stay, but also the costs of that hospital admissions.

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So clearly it's expensive to have the opiate adverse events following surgery.

Now, we also know there's increasing evidence that patients stop using opioids after minor or major surgical procedures. this is a recent study that shows about 8 to 10 percent usage of opioids following an acute episode, and they continue to use opioids in some of the major procedures. A colectomy is even higher. So clearly, if we can avoid that, potentially we might be able to reduce the problem of prolonged opioid use.

Opioids within the hospital also can be deadly. This is a study that Frank Overdyk and I, we looked at, again, the PRIMIER database, looking at an incidents of cardiorespiratory pulmonary arrest in the hospital. And we looked at both surgical and medical patients, and clearly there are many patients who are on opioids. Many patients are on sedatives. The rate of cardiopulmonary respiratory arrest is listed down here, and you can see medical patients and surgical

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patients.

Now, if you have opioid and sedative in combination, your rate of cardiopulmonary respiratory arrest goes up substantially, in this case almost about 4 times. And if you do a multivariate analysis, again, whether it's surgical or medical patients, typically if you add sedatives and opioids together, your rate of cardiopulmonary arrest goes up at least twice. So clearly, it is something that we could potentially better manage by either reducing opioids and maybe better monitoring. So certainly, there are a number of strategies there.

Clearly, treating pain is a balancing act. On the one hand, you under trying to reduce pain; on the other hand, you are trying to manage the side effects of the drugs that you use.

Now interestingly, from the patient perspective, if you were to ask patients what do you really want in terms of pain management, what would make you happy after surgery in terms of pain management, you would think that, well, I want to

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have zero pain. But in fact, it turns out that is really not the case.

This study we conducted a few years ago, really asking patients who are on PCA, on opioids PCA, we asked them what are the things that make you decide to press that pain button? Many of you who do pain rounds, you go to see Ms. Smith that complain 10 out of 10 pain. And Ms. Smith has a PCA button in her hand, and she hasn't pressed the button for the last 2 hours.

You go to Ms. Smith and say, Now, I understand you complain of a 10 out of 10 pain. You know that you have that pain button in your hand that's supposed to treat your pain. She says, "I know. I've got a pain button." I say, "Why haven't you pressed it in the last hour or so?" Then you begin to hear from Ms. Smith the reasons that determine her pressing the button versus not pressing the button.

So when we're presented with a scenario about -- let me give you two scenarios. One scenario is where you have good pain relief but it

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comes with moderate vomiting versus just for pain relief, not quite as good but no side effects. And you can see the majority of patients actually prefer not having the side effects and managing somewhat some degree of pain. "I don't necessarily need to have no pain."

Likewise, another scenario, severe constipation with excellent pain relief, great pain relief, but you can't open your bowels, versus just good pain relief with mild constipation. And again, the majority of patients -- as you can see, from the patient perspective, they would rather avoid the side effects because they know that these side effects are annoying, nausea. Ms. Smith says, "Well, when I press the button, they make me feel drowsy, they make me feel loopy, and I just don't like it." So they trade off between efficacy and the side effects profile, and that's what we do all the time.

Now, we know there are a number of non-opioid analgesics. As you know, pain coming from peripheral to the central up to the brain at

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the same time, at every point in time or every path of that pain pathway, there are certain non-opioids that certainly can be effective, local anesthetic, nonsteroidal, as well as the alpha-2 agonists, and obviously some of the other drugs, ketamine and acetaminophen. So there are a number of non-opioids that we can use to minimize the amount of opioids.

So the question is this, how can we better effectively treat pain? And again, certainly now with regional anesthetic techniques that we employ -- and if you are having a good block, you really don't need anything else. For example, if you have a good working epidural, there is really no need to add additional opioids. But we always seem to think that we need some opioids interoperatively.

I often walk into the room where either nurse anesthetist or residents, they give 50 mgs of fentanyl every half an hour. And they say, "Why do you do that for?" "Well, you know, pressure goes up a little bit and heart rate goes up. I think

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the patient is in pain." But the patient has a good working epidurals. So sometimes you've got to think about how do we best give opioids interoperatively and postoperatively.

So what are the objectives that we are trying to accomplish in a patient having major surgery, trying to manage their pain? I think there are really three aspects. One is to keep patients comfortable, to try to make sure that they are at a level they can actually go about either doing their rehabilitation. They can get out of bed and walk around, and they are able to sleep at night.

So to keep them comfortable and at the same time trying to encourage recovery because they're not going to be staying in a hospital for a long time. And nowadays, most surgical procedures, either they are done on the same day or they stay one night, or a couple of nights. It's rare for patients to stay in the hospital for 5, 6, 7 days at a stretch. I think we have better surgical techniques. We manage pain better. And we want to

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get them out quicker with this enhanced recovery concept, at the same time minimizing the side effects.

So I think this concept about encouraging postoperative dreams -- what does postoperative dreams stand for? Well, dreams stand for drinking, eating, analgesia, mobilizing, and sleeping. Now, if you can do all of these 5 things, number 1, the patient can get out of the hospital; number 2, then you have a good surgical recovery. And this is what is enhanced recovery concept, trying to promote getting the patient up and about as soon as possible, have a reasonable good management of pain to reduce some of the side effects, get them to eat and drink, and get out of the hospital.

I just want to share with you in this context of enhanced recovery, I think it is now starting to become I believe the standard of care in the U.S. In fact, it has been done in many other countries.

This is a study that we did at Duke, basically just to look at how does integrating the

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enhanced recovery program help our postsurgical patients. We looked at colorectal patients undergoing colorectal surgery, either open or laparoscopic. This is our analgesic regimen here. We did a thoracic epidural, an open tap block for the laparoscopic approach, and a variety of a non-opioid multimodal analgesics, together with antiemetic prophylaxis, and using that as a management strategy and trying to reduce intraoperative and postoperative opioids.

Again, this is not just pain control. There are other aspects with enhanced recovery, but we did see a significant reduction in length of stay on average, about 2 days, even for laparoscopic procedures.

Now, if you look at pain specifically and opioid sparing, on the left side of the graph here shows you the amount of morphine equivalent during surgery and after surgery. And again, you can see that with a multimodal approach of pain management, with a good working regional thoracic epidural or tap block, we can significantly reduce the amount

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of opioids I give patients.

Now, the other interesting -- that we found was that you often hear surgeons -- any surgeons in the room here? You always hear surgeons say laparoscopic procedure is a minor procedure, and it doesn't hurt. Right? There's no need to give any analgesic. But interesting, when we looked at the degree of pain, there is really not that much difference between the open approach and the laparoscopic approach. The duration may be shorter, but the pain intensity is actually pretty intense, even though with the little keyhole surgery.

Again, the enhanced recovery group had a better pain score. I just want to focus that in terms of bowel recovery, again, minimizing opioids enhances bowel recovery because we short opioid reduction by about fourfold in the enhanced recovery group.

So the last part of my talk is to really look at how can we assess this opioid sparing. And I think it's a question that we don't really have a

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good answer. There are really two ways that you can assess opioid related side effects and opioid sparing.

What is the impact of opioid sparing? Now again, reducing 30, 50 milligrams of morphine equivalent isn't really a big deal. Right? Opioids, morphine is inexpensive. Fentanyl is inexpensive. But what is more important is can you demonstrate a corresponding reduction of side effects, which I think is much more difficult to treat. And also, those are the ones that prolong the hospital stay, and patients tell us that they don't like it.

So there are objective and subjective ways to assess that; objective, certainly in the incidence of vomiting, time to GI recovery, and the need for any rescue medication for opiate adverse events. So these are fairly objective.

Then there is also from the subjective perspective, from the patient-reported outcome -- which certainly is important because this is what patients tell us that they like or

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dislike. There are a number of scoring systems trying to assess that on the patient-reported outcomes of opiate related side effects, and I just want to run through some of these with you.

So one of these is this postoperative Opiate-Related Symptom Distress Scale, which was originally developed in chronic pain by Russ Portenoy. A number of years ago we thought, well, could we adapt it in the acute postoperative setting. And when we are doing the Cox-2 trials and we're trying to validate this instrument -- and essentially, this instrument looks at opiate related adverse events: nausea, vomiting, constipation, diarrhea, difficult passing urine, some of these post-op events that patients may experience.

We collected the data over the next 10 days after surgery and really just tried to see is that a good instrument to demonstrate opiate sparing, and more importantly opiate related adverse events.

So we did a validation study. For the scale, we measured 3-dimension. We measured the

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frequency of the adverse events, how frequently does it happen; how severe was the adverse events, if you have either minor nausea or very severe nausea; and how much does it bother the patient because some side effects may not bother the patient that much; so I think this degree of what is the bothersomeness of the side effects.

We looked at these three dimensions, and patients tell us over the postoperative days after surgery and showed that they correlated with the opioid reduction on opiate doses. If you were to plot -- this is over 10 days after surgery, and this is the clinically meaningful events, so these are a combination of frequency, severity, and bothersomeness, and this correlates with opioid consumption.

Certainly, if you look at opioid consumption here in the open circle, probably within the first 3 to 4 days, this is where most people consume most of the opioids. Beyond that -- and again, these are patients undergoing lap chole. So beyond that, most of the people just tail off, do not really

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need that much opioids. And again, you can see the adverse events frequency correlate pretty well with the opioid doses.

So perhaps this could be an instrument to try to assess the degree of opioid sparing and also what does it mean from the patient perspective.

Now, there are other patient-reported scores that have been validated and published. There is the quality of recovery score, and there are 15 questions and another version with 40 questions by Paul Malz [ph] and his group from Australia, essentially looking at not just opioid adverse events but the general recovery in terms of how well you sleep and how do you interact with your friends and relatives. So again, that has been validated as a postoperative recovery patient-reported outcome scoring system.

More recently, a group came together to look at all the trials that have been published related to patient-reported outcomes. Using a modified Delphi technique, we went through a number of iterations to look at what are the things that we

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felt that, first of all, is valid as a scoring system. Is it reliable? And more important, is it feasible to be done in a clinical setting? And what does it mean to the patients?

So we went through this iteratively and then scored this between zero and 10. So the higher the score means the more validity and more feasible it is to collect, and more patient centered [indiscernible] is the score. Again, pain is certainly an important outcome that patients care about. Nausea and vomiting are other ones that postoperatively happen commonly, and I think is something that's important to avoid; the quality of recovery score as well as time to GI recovery because that also predicts the length of stay; the time to rehabilitation and mobilization because the earlier you can get a patient out of bed usually means they can get out of the hospital.

Now, if you were to go and visit your patient postoperatively, those patients that stay in the hospital, you will find that about 50 percent of the time, the reason they occupy a

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hospital bed is because their bowel is not working. When a bowel is not working, they ain't going anywhere; they stay in the hospital. But as soon as bowels start to move, that is when you are able to discharge patients usually the next day. And obviously, the other aspects, sleep is also important.

Many professional societies, including the American Society of Anesthesiology, advocate this concept of the multimodal approach, giving non-opioid analgesics. We know that it works. We know that it can potentially reduce opioids. In fact, with the enhanced recovery protocol, advocating not only multimodal but also reasonable technique, a number of procedures now can be done without opioids. Opioid free is certainly achievable if you've got a good regional block, and then post operatively you can probably just get away with nonsteroidal or either non-opioids.

So the challenge is how does this translate into a company who wants to approve an analgesic and demonstrate the value of non-opioids? This is

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where I think, hopefully, this group will come up with some recommendation to the FDA because I know the FDA doesn't really have an answer. So I hope that this group will come up with some recommendations to be more able to validate opioid sparing and what does it mean. And I think just reduction of morphine is really not the right answer because I think it really means more than that.

I think with that, I'm going to conclude. I am 25 minutes. Thank you very much for your attention.

(Applause.)

DR. KROENKE: Again, we have time for maybe a few questions. [Inaudible - off mic].

(No response.)

DR. KROENKE: Okay. Thank you.

DR. GAN: Thank you.

DR. KROENKE: So our third presentation is going to be by Nathaniel Katz, who is president and CEO of Analgesic Solutions in Massachusetts. He'll be talking about opiate sparing trial objectives

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and outcomes for chronic pain.

Presentation - Nathaniel Katz

DR. KATZ: Good morning, everyone. Third Speaker before break, not a great position to be in, but I'll try to keep you guys awake. At least look like you're awake, if you don't mind. It will make me feel bad if I see people actually nodding off. Not paying attention is okay.

My presentation will be somewhat in the spirit of TJ's presentation in that I'll be taking more of a patient-centric view of opioid sparing. And even further than that, I'll take a clinical trial centric view over the patient view, and then hopefully come up with a concept of opioid sparing that will help us conduct the rest of the meeting in a useful away.

I thought what I would do is actually start from the specific and build to the general, which I think can be more helpful than starting out with the grand concepts. So I thought I would put a few clinical trials scenarios on the table of how we might address this concept of opioid sparing from a

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clinical research perspective, focusing again on chronic pain, and then pointing out what the hypotheses are that could be generated by various research studies. And then we'll see how far we get from there in terms of building a concept of opioid sparing.

Scenario number 1. You take a bunch of patients with chronic pain who are either not on opioids or maybe they're on a little bit of a smattering of short-acting opioids, and you put them on some non-opioid analgesic and compare it to placebo. You let everyone take opioid rescue. Maybe let them take as much as they want or at least enough of it that you can measure a difference between these two groups.

A classic example of that might be Vioxx for chronic low back pain or something like that. The idea is that, well, my non-opioid analgesic is going to take over some of the pain control, sort of as TJ said a moment ago with epidural, local anesthetics, and things like that, taking on some of the burden of the pain control. And then the

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patients won't need as much opioid rescue. Their doses will be lower. As consequences of their dose being lower, they'll have fewer opioid related side effects; although how you measure that, TJ started to talk about, and I'll continue to talk about that in a moment.

The hypothesis that a study like that can address would be just that; do these patients have lower opioid doses? And as a consequence of their lower doses, do they have a lower burden of opioid related adverse effects? And that does bring up a first philosophical problem that we will have to deal with that both Eric and TJ have already alluded to, which is what do we mean by opioid sparing?

Is it just reducing the dose? Is that what we mean by opioid sparing? So this group is on 10 milligrams and that group is on 9 milligrams, so have I accomplished something? Or maybe I have to lower it from 10 milligrams to 1 milligram to accomplish something. Is it just about the dose or does the concept of opioid sparing only have

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meaning insofar as we can show some direct patient benefit of that opioid dose reduction? Or do you need both, some combination of both?

So that's scenario number 1 and the benefits of what we can learn and that scenario, but also some of the kind of philosophical challenges posed by that scenario.

Let's talk about a second scenario, scenario 2 here. Patients with chronic pain are coming in on some substantive doses of opioids already. And again, as in the first scenario, you're randomizing them to some non-opioid analgesic regimen. You're trying to take over some of the pain control that those opioids are presumably providing to those patients, compare it to some placebo or some control condition.

But here, in contrast to the first scenario, you're trying to get people off their opioids or at least trying to lower their doses. And you're doing that by using some other treatment to maintain their pain control. So the hypothesis that can be addressed in a study like that is that

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the patients on the analgesic arm can lower their dose.

So now you're talking about maybe mean dose between the two groups at the end of the study or you can get some certain percentage of patients off. So maybe 40 percent of the patients in this arm came off, but only 10 percent of the patients in that arm came off. And you have this concept that we all resonate with, that the patients don't need opioids anymore at all, and Eric alluded to that as well.

So that brings us to another philosophical question that we'll have to deal with, which is do we think of the concept of opioid sparing differently if I just lower your dose versus if I get you off completely? Is getting you off completely enough in terms of opioid sparing? Is that by itself intrinsically an accomplishment or do I have to show that I've actually reduced your nausea or constipation or something like that?

I think what I would put on the table for your consideration is that I think getting people

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off of opioids has intrinsic value. Although, again, we get back to this concept that we have to keep a grasp on, which is that getting people off their opioids or lowering their doses doesn't really have any value to the patients unless we're maintaining their pain control, as Eric said earlier.

That seems like a really obvious concept to me, at least as a clinician, but you'd be surprised how hard it has been to convince some pharmaceutical companies that just lowering your opioid exposure but letting your pain get out of control, that doesn't actually have value to the patient. And a number of companies have gone pretty far along the clinical development path until they finally crashed and burned because of the obviousness of that issue.

So as we define opioid sparing, we're going to need to consider whether sparing somebody their opioid dosage is meaningful unless we're also sustaining their pain control. And personally, I think it's not.

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Scenario number 4, here we bring patients in with chronic pain and we put them on some standard opioid, and then we're developing some better opioid. What does better mean? Better means maybe something like it can give them just as good pain control but fewer side effects. That would be a huge societal benefit.

As TJ mentioned earlier, in the chronic pain setting, as in the acute pain setting, patients are usually trading off some degree of side effects for some degree of benefit. The patient who is absolutely free of side effects, I don't think I've ever seen that patient in the chronic pain a setting. There is always some degree of side effects. If there was some better opioid, that would be great.

So here, it's not about dose in this scenario. This scenario doesn't care about the dose. This scenario cares about the patient and whether the patient maintain, has a better therapeutic index of their opioids; let's just say same pain control but fewer side effects.

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Now from a measurement perspective, if I'm measuring the burden of opioid related side effects, the tools that I'm going to use in this scenario are basically the same as in these other scenarios. I'm going to have some measure of opioid related side effects or safety issues with opioids. But the difference here is it's not about the dose anymore.

So this raises another terminological and philosophical question for us, which is that the concept of opioid sparing, does it include this? So if the definition of opioid sparing is reducing the clinical burden of the side effects and tolerability issues imposed by opioids, then the definition of opioid sparing includes this syndrome. But if the definition of opioid sparing is limited to let's just say a dose-centric view -- I'm lowering your dose, and then maybe there's some beneficial consequences of that -- then this scenario would not be included in that definition. So this is something we're going to have to decide in the next day or two.

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Then finally, the fourth scenario that I'll put up here -- and let me just state the obvious, that these scenarios are not exhaustive. There are all sorts of intermediate and different cases as you could imagine. But I think they illustrate -- the reason I put these scenarios here is because they force us to grapple with what we mean by opioid sparing.

So here you take a bunch of patients on opioids -- maybe they're not even on opioids; let's just say they are -- and then you add some kind of opioid enhancer, or you don't. You put them on placebo. What do I mean by an opiate enhancer in this case? I mean something that improves the pain relieving aspect of the opioids but doesn't worsen the side effects; or the opposite is good enough for me, too, that patients can maintain their sense of pain control but it reduces their side effects somehow.

This may seem like a weird thing, but actually this has been a very commonly approach theme in drug development over the last 25 years,

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particularly with NMDA receptor antagonists, things that purport to modify the way opioids either act on the receptor or downstream effects after binding to the receptor. This is actually being done a lot.

Maybe some of you are old enough to remember the MorphiDex program. Yeah, remember that? Dextromethorphan was an NMDA receptor antagonist back in the day -- I don't know if it still is -- and was purported to reduce the side effects of opioids without a tampering with their benefit. And that was going to be a great thing because all of the preclinical trials sung the praises of this concept to the heavens, and of course it was going to work in practice, but 3 pivotal trials later, it never panned out in the real world, and it was gone. But the concept is still a very kind of established concept.

So here, you could imagine looking at the concept of opioid sparing in a couple of different ways in a scenario like this. Maybe you can reduce the amount of opioids you need to maintain the same

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amount of pain control, but of course nobody cares about that if the patients have the same amount of side effects. See, you can't get away from this attachment of the pain relief to the side effect and still be thinking about the patient's welfare; or you can forget about the dose and just add your opioid enhancer and reduce the side effects. And again, from a patient perspective, that would be a huge benefit.

So are both of those opioid sparing or is it only opioid sparing when we reduce the dose and maintain the benefit? So those are some issues that are eliminated by this exercise if considering scenarios.

So I think if we learn anything about opioid sparing from even just the thought experiment of considering those scenarios, again, we learn that the concept of opioid sparing, if you're taking a patient-centric view, is meaningless without sustaining pain control.

Of course, to the points that Eric raised earlier, if we're considering opioid sparing from a

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societal perspective and we just want to reduce the extra medicine in people's pill cabinets because that's going to address the abuse and addiction and all that, if we believe that -- and I do; I do believe that, and I do think that that is important -- then that's not a patient-centric view of opioid sparing. That's a societal-centric view. And when we come to define opioid sparing, we're going to have to decide which of those potential elements of a definition of opioid sparing we choose to include because it makes a big difference in how you measure whether you've achieved it or not.

My own patient-centric view, the view that I would put on the table for consideration, is that opioid sparing can be conceived of as decreasing the burden of opioid related adverse effects on patients while sustaining their pain control. That's what I think opioid sparing is from a patient-centric perspective. And that can be accomplished in essentially two ways, and one is PK and one is PD; a big surprise.

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So you can reduce opioid side effects by reducing the amount of opioids people need; that's one way. If you only need half the amount because you're on Vioxx, well, great. I've spared you both the amount of opioids and the side effects. Or maybe modifying the PK profile.

If I've got some kind of extended-release opioid that enters the central nervous system more slowly or has a lower Cmax, maybe I can reduce your peak dose side effects that way; maybe even without even altering your overall dose of your overall exposure. That would be a way of producing what I consider opioid sparing, which potentially is reducing the burden of side effects, or of course get patients off completely. That's pharmacokinetics in a sense as well; or you can spare patients the burden of opioid side effects, if you like that notion of opioid sparing, by altering the pharmacology of the opioid either through creating a new molecular entity that has fewer intrinsic adverse effects while still maintaining benefit, or adding some kind of

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enhancing thing that that modifies the pharmacology.

So why am I going through all that? Because it forces you to think about whether your notion of opioid sparing is about sparing the burden of opioid adverse events through these strategies, some of which involve reducing doses, but some of which surely do not; or are you going to have a more narrow dose-centric view of opioid sparing, which actually takes off the table these more pharmacologic based approaches.

Finally, I haven't talked much about what I even mean by adverse effects of opioids, and TJ began that discussion, and I'll carry that on a little bit further. I'm using this concept of opioid related adverse effects in kind of a loose and general way, and it includes actually quite a lot of the things that are different, one from the other, and there are some other conceptual issues that are not addressed here yet.

So here, Jen, is a proposed definition of opioid sparing that we can perhaps dismantle and

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put together, back again, as a group later because the paper that we produce will be useless unless it has some definition of what actually the paper's about, opioid sparing.

What I would propose, although it really does not fully accommodate the societal view that Eric brought to the table, is that it could be something like the following. And again, everyone's all about, gee, do we really need a comma there and maybe it should be a hyphen, but just think about the concepts for a second, that we have to decide whether we are going to be in this definition or not.

It's "the implementation of an intervention to reduce the adverse effects of opioids on patients while maintaining or enhancing pain control by" -- and here is like a listing of the different types of interventions that I actually had on the previous slide that could be contemplated by this definition -- "decreasing the dose, getting it off completely, modifying the pharmacology," et cetera, et cetera.

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So this is a definition of opioid sparing that deliberately is not just focused on reducing the dose, but we may decide as a group to reject that.

Now to the question of what are -- now I'm going to extend TJ's comments about acute pain to the chronic pain setting, and what actually are the adverse effects of opioids that we might want to measure if we're going to claim that we've reduced them.

First is the individual, what you might call the nuisance side effects, although too many patients, that's a lot more than a nuisance. Vomiting all day is not fun. And actually, as TJ said, you'd prefer more pain for less vomiting in many situations. So there's the long list that TJ mentioned: nausea, vomiting, et cetera, et cetera.

Now here's a very important conceptual point, and this is probably the most important thing that I'm going to bring to your attention during my presentation. So if you're going to just pay attention to one issue during my presentation,

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this is the one to pay attention to, which is are opioid side effects as a whole one thing, or are they actually a mish-mosh of different things?

So is nausea, nausea; and vomiting, vomiting; and dizziness, dizziness; and sedation, sedation; and we have to measure each one individually and show that when we are reducing the burden of opiate adverse effects, we have to be specific about which one we are reducing and which one we're not; or can you consider all of these things together as one thing?

Are we reducing opioid related side effects, and what are the implications of that? And I think the people in the room who are wondering about this know who they are. So this is very important because if you don't believe that opioid side effects are a single thing, then talking about we reduced opioid side effects, that has no meaning and probably wouldn't end up in a package insert, I wouldn't think, because we don't like meaningless things in package inserts; whereas, if you think that they're all individual things and that each

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one's going to have to be dealt with on their own.

So this is an important conceptual issue that I will dwell on it at some length in the next one or two slides.

Back to the list of what the opioid adverse events are in chronic pain. Endocrinopathy, I think probably most people are familiar with that these days, but this is actually probably the most common serious toxicity of long-term opioid therapy, the endocrinopathy, although it's the lowest on the list in terms of what people talk about.

This probably occurs in the majority of people on long-term opioids; not the minority, the majority. If you care about things like infertility and sexual function, then you care about endocrinopathy -- and osteoporosis and compression fractures, then you ought to care about this, but it actually has gotten very little attention.

TJ mentioned overdoses already; this is a big problem. And then the panoply of problems that

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fall under the abuse and addiction. This is also not exhaustive, but it's a list of the major kind of categories of adverse effects of opioids that we worry about in the chronic pain setting.

So let me get to the issue of whether the opioid side effects are one thing or they're just a jumble of different things. When I say one thing, the word that comes to mind is -- we already have a word for that, which is "syndrome." This is the Merriam-Webster definition of a syndrome, which is a group of signs and symptoms -- it can be signs; it can be symptoms -- that occur together and characterize a particular abnormality and condition.

It has a lot of impact on measurement. I'll give you an example. The WOMAC pain subscale is an example. You've got 5 items there. That pain subscales is accepted as a validated measure of one clinical concept, which is the pain in patients with osteoarthritis, the hip or a knee. But the 5 items are asking people about different things. One is pain on activity. One is pain on standing.

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One is pain on sleeping. One is pain walking up and down stairs.

So you're measuring one concept, which is pain in osteoarthritis, but you're measuring it -- it's classical test construction theory. You measure it most reliably by asking patients about different manifestations of that same underlying concept. Pain on sleeping is not the same as pain on walking on a flat surface. Those are different things, but they're thought to be measures of the same underlying concept.

But if you're talking about something like the WOMAC scale in its entirety, you're talking about one group of items that measures pain; one group of items that measures stiffness, which is a different thing, different concept; a third set of items that measures physical function. That's a different thing, and you don't add them up. You don't combine them because they're not measuring the same concept.

So from a measurement perspective, psychometricians are always grappling with this

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issue, is what does it mean to have different questions that measure the same thing or different groups of questions that measure different things?

So back to the opioid thing, it's obvious that you have the same issue here. Are all these things one underlying concept or are they just all different things that cannot be combined into a single measure?

Now, TJ has already answered this question from the perspective of acute pain, which is that they have developed a scale of opioid related side effects, which you wouldn't have developed a scale like that unless they were all measures of the same thing, and I'll deal with that a little bit further.

Now, because this issue is so important, even though my time is going by quickly, I'm going to try to give like a warm and cozy example of this to get people comfortable with the concept of different elements of a syndrome because it's more controversial with respect to these opioid side effects.

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Here's another syndrome, a collection of signs and symptoms that are all different aspects of one underlying process, which is the acute opioid abstinence syndrome, opioid withdrawal. Some people get nausea, some people get stomach cramps, some people get muscle twitching. These are 10 of the core features of this syndrome. And in fact, these are the items on the SOWS gossip scale of measuring opioid withdrawal, which became a scale because these are the cardinal manifestations of opioid withdrawal.

So if you do factor analysis, blah, blah, blah, you'll learn from a psychometric perspective that these in fact can be considered different elements of the same syndromes. If I add all these things up and create a score, and I do a clinical trial where, gee, in this group, the opioid withdrawal was less than this group, if you add these things up and the overall score is less in one group than another, you would say that that group had less opioid withdrawal.

Does that mean that feeling cold was reduced

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compared to one group, or that yawning was reduced, or that aches and pains was reduced? Not necessarily. Some people will have less nausea. Some people will have less aches and pains. But if you add up their opioid withdrawal score, they have less opioid withdrawal, and that's accepted as a concept.

In fact, you could take this even further and you could imagine that maybe there's some drug that reduces opioid withdrawal, and clearly the opioid withdrawal scores are lower in one group than another, and statistically significant, and clinically significant, and all that stuff. But maybe because of the nature of that one drug, it actually really doesn't reduce. I don't know what's a good example. Palpitations? Maybe it actually produces tachycardia as one of its side effects, and maybe palpitations would be even worse in the group with less opioid withdrawal than the other group, and maybe even that would be statistically and clinically significant if you picked out that one item.

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So would you say that the group had experienced lower opioid withdrawal or not? That's the philosophical question. I would. And maybe if I was really smart, I would say, gee, it reduced opioid withdrawal as a whole, but look, you might want to know that there's actually more palpitations, or not lower palpitations, or whatever because blah, blah blah, and then we could be clever and really understand the pharmacology of the drug. But I don't think you would say it didn't reduce opioid withdrawal. I think you would say it would.

This is a huge issue with respect to opioid side effects as a consequence of opioid sparing, because it's obvious what the analogy is that I'm trying to make here. You're all piecing this together in your minds. If we are going to say that we've reduced opioid side effects, do we accept that as a syndrome, as a totality composed of these different elements, or do we require that each one of these things be addressed independently because they're not combinable?

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If we're treating pain of osteoarthritis of the knee and we do accept that the WOMAC pain subscale is a measure of that, what if there's a drug that doesn't reduce pain on staircase climbing? Which is item 2 in that scale. Do we reject the notion that the drug reduces pain of osteoarthritis? We don't.

So how do you decide if something is a syndrome or if it's a jumble of different things? There are ways of deciding that, and psychometricians have been doing this for a hundred years, and we really don't need to reinvent that wheel.

We did a development program on another opioid side effect scale, similar very much to the one that TJ mentioned. We also did an acute pain. This was not done in chronic pain. But the reason I'm mentioning it is because this program incorporated the different psychometric elements that you would need in order to decide whether something was one thing or a bunch of different things.

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I won't belabor the whole program, and I'll be happy to share this information with people. But the bottom line is the things that you would do to decide whether different elements were part of the same underlying concept -- such as exploratory factor analysis and internal consistency of the items, and divergent validity and convergent validity with companion measures, and all those kind of psychometric things -- led to a clear conclusion, which is that these seemingly different opioid side effects do actually fall on one factor, and they are actually one thing from a psychometric perspective.

So I believe that we can comfortably view opioid side effects as one concept with different manifestations like the WOMAC pain subscale has different items that reflect different aspects of that same underlying concept. It doesn't mean you can't measure nausea independently; of course you can. Nausea and constipation are not the same thing. They're not. But they are different manifestations of one common unifying concept.

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That's the point. That was worth spending 10 minutes of my time on.

Now I'm going to talk a little bit about measurement. I made a list of the main sort of types of opioid adverse effects that we should consider in the chronic pain setting, and now I'm going to talk at a high level of how one can go about measuring those things because you can't do a clinical trial unless you know how you're going to measure whatever it is that you want to measure. And I'm going to go through some of the categories of adverse effects that I mentioned earlier.

If you're talking about measuring individual side effects -- let's say I'm going to spare these patients the burden of sedation from opioids and that's what you're focused on, then there are different options that you have. Of course, if you think you're going to lower sedation by lowering how much of a dose somebody needs, well, it would be a good idea to show that you actually did lower that dose.

You'd be shocked and appalled at how many

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clinical trials are done that include opioids in either acute pain or chronic pain, where the opioid consumption is literally not measured in any kind of understandable way. So that seems obvious, but trust me, it's not always obvious. Maybe some of these individuals side effects, they're going to be some kind of objective test, as TJ said. For most of them, they're not, but it's certainly worth considering.

Like if you're interested in endocrinopathy as an adverse event of opioids, then, yes, you will be very heavily focused on the laboratory measurements of that, as well as the clinical consequences. But for others like nausea or sedation, there's no laboratory tests. It's a checkbox, though. You need to consider it.

Then there might be single-item instruments of the single side effect, like how sleepy are you? Or you could imagine what's normally more useful than a single-item instrument is a multi-item instrument focused on a single side effect. And people all so often get this confused. There are

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multi-item measures of single side effects -- sedation, nausea, et cetera -- and there are multi-item measures of multiple side effects like multi-item measures of opioid side effects in general. So if we're going to have a coherent discussion, we should bear those distinctions in mind.

Then finally, you can try to capture these things just by counting adverse events. And I think we all know, and this group has discussed many times, that that's generally the worst way of doing that because you can often have clinically significant differences in the burden of tolerability that are not picked up by just trying to squint your eyes at the adverse events tables that we normally get access to; although there are clever ways of dealing with adverse events that are probably better than the standard charts.

What if you're interested in measuring the syndrome of opioid side effects, the total concept that I've been belaboring? Opioid dose is kind of a start. Laboratory tests, not really. You can

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imagine single-item instruments -- and these do exist and these have been used -- how much are you overall bothered by side effects, things like that; not a great way of measuring this. Or you could imagine multi-item instruments of the type that TJ introduced for acute postoperative pain.

I'd be interested if somebody knows different. As far as I know, there's actually no opioid side effects scale that's been validated in the setting of chronic pain, which is kind of shocking because Bob and I did a trial that we published in Spine in 1998, back in the day, where we invented our own opioid side effects scale. But we didn't -- truth be told -- work very hard on validating at that time. And even though it worked, I must point out, I don't think that there's ever been like a start from scratch development and validation of a scale like this from chronic pain. But if anybody knows of one, let me know.

Memorial Symptom Assessment Scale that TJ -- if you actually take a look at these scales,

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for one reason or another, they all have substantial limitations in this setting. And again, you can try to just count up side effects, but that doesn't work very well.

Well I've only got a minute or two left, so I think I'm going to skip this actually very beautiful story about how you can do better with just passive capture of adverse events. It's a project that I'm very proud of, but in the interest of time I'm going to skip it.

This is actually more important, which is where do we want to end up at the end of this meeting? You will recall that the first IMMPACT paper ever done was on core outcome domains that were thought to be important in clinical trials. So I think there's sort of an analogy here, which is what are the domains of opioid sparing that we might be interested in measuring in a clinical trial? Then once you decide what those are, the second IMMPACT paper was, okay, what are the actual validated measures of those domains that we could consider incorporating into a clinical trial? We

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can imagine building a similar kind of matrix here.
So this is just cut and paste from my previous slide. Here are some suggested, what you might consider opioid-sparing clinical domains or clinical concepts; individual side effects, the syndrome as a whole: endocrinopathy, abuse, addiction, et cetera, et cetera.
Then here are possible measurement approaches, single-symptom questionnaires: a nausea questionnaire; a vomiting questionnaire; opioid side effects questionnaire as a whole; laboratory tests; measures of abuse; and passive capture of adverse events. And you can imagine doing some kind of a matrix that you populate, where you list where there are available and validated measures of these different domains and where there are not. And this I think could be a good exercise for us to engage in because the people actually doing the clinical trials, this is actually what they're going to need.
I think I'm going to wrap up. There are other interpretation or reporting issues, and we'll

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get to those later. So to summarize, patients suffer a lot from a variety of different types of adverse effects of opioids that they trade for some degree of pain intensity reduction. Interventions to reduce these adverse effects certainly could benefit patients as long as you account for the pain intensity and don't ignore that, as has been so often done.
There are a variety of approaches available to measure these benefits, some more validated, some less validated. They all have their strengths and limitations. There's no magic bullet here. And I do believe that identifying and remediating the gaps in the table that I showed you a moment ago could help us on our way of supporting clinical trialists and people who are developing these approaches, and convincing the world that these approaches do have these opioid-sparing benefits.
So that's what I got for you. Thanks so much for your attention.
(Applause.)
DR. KROENKE: Any clarifying questions?

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Yes?
DR. KATZ: Deb, can you both use your mic and tell people who you are?
DR. STEINER: Hi. I'm Deb Steiner, and I'm from Cambridge, and I'm in drug development. I've been in clinical development for quite a few years.
So my question -- and this is coming from perhaps a naive viewpoint or just a different viewpoint because I've not designed opioid-sparing trials, although I'm fascinated by them. In the current environment in which we are with this opioid epidemic, I guess the statement that we need to be looking for the same pain relief and the same side effects or acceptable side effects, well first of all, as a drug developer, it's very difficult to get both. You want efficacy and you want to have low side effects.
I'm thinking if we can come up with something which has -- the side effects are not worse, or they're not terrible, or at least it's safe, and there's at least comparable efficacy, then that's a home run.

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Yeah. I think what you're saying, Deb, is if we came up with some strong non-opioid analgesic, which of course has been a holy grail for since the U.S. Civil War --
(Laughter.)
DR. KATZ: -- right -- from the first prescription opioid epidemic that we had. We're in the second one, I think everybody, everybody knows. Yes, that's been a holy grail for a long time. So from a societal perspective, if you could reduce the prescribing of opioids by some large percent because you've got other effective strategies available, yeah, I think that that's critically important, and that would the holy grail of opioid sparing from a societal perspective.
DR. KATZ: Yes?
MS. WENTWORTH: Hi. Kerry Wentworth.
DR. KROENKE: Oh, I'm sorry. Torsten was next.
DR. MADSEN: I'm Torsten Madsen. I'm with Apitnyx. This is just a pragmatic question from a clinical guy who does clinical studies. What is an

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acceptable timeline for us in the drug development to show all the magic stuff you had on the slides?
(Laughter.)
DR. MADSEN: 12-week, 4-week studies or where? And second, that I have -- it's a tripartite question -- is you didn't spend a lot of time talking about cognitive side effects of chronic opioid abuse. Would that be an acceptable endpoint to include also in such trials? And can you envision biomarkers being included as acceptable endpoints to claim opioid-sparing benefits; i.e., you mentioned testosterone or the like. Should we think in that direction as well as drug developers?
DR. KROENKE: So to reiterate -- actually, you had three parts to that question. This will be our last question before break. I see about five other hands, which we [inaudible - off mic].
I heard the question, should cognitive count as well? I heard the question how long should the trials be [inaudible - off mic]?
DR. KATZ: Biomarkers. So duration, I think

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it will be in the details. Small proof-of-concept studies can be shorter, but if you're going to make claims about long-term use, they need to be longer. Typical is three months, as you know, but of course there are always calls for longer studies. So I think I'm going to leave that piece with that general answer.
In terms of cognitive function, neuropsychological side effects, I was debating whether to put that on the slide of adverse events. Yes, of course, that is a significant issue. Actually, the studies of the long-term cognitive effects of opioids and the treatment of chronic pain give you kind of mixed signals. In fact, we did a study on that, too, and there have been others suggesting that there really aren't significant impacts of opioids on cognitive function in patients with chronic pain in general. But there are issues about did we measure it the right way and all that. But yes, if you could have treatment that reduce neurocognitive burden, certainly that would be a benefit of opioid sparing

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or improving the risk-benefit ratio of opioids.
The third one was the biomarkers, and I think, yeah, if the biomarker is validated as a surrogate for whatever clinical benefit you're trying to accomplish, then, yes. And if it's not validated, no.
So for something like endocrinopathy, where surely 3 testosterone levels are validated as a measure of a patient'[s endocrine health, I would imagine that, yes, that would certainly be an important endpoint. Whether you would also have to demonstrate clinical benefit, probably. I think it just depends, like in any other situation, on the status of validation of the biomarker.
DR. KROENKE: We have 25 minutes for break. We should rejoin probably at 10:30 [inaudible - off mic].
(Whereupon, at 10:07 a.m., a recess was taken.)
DR. KROENKE: We're going to get started. Now we're going to have two presentations, and then we'll mention how lunch is going to work. But

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we're going to have people have an opportunity to get their lunch, and then part through, we'll rejoin and have our discussion.
There were a lot of questions that came up this morning where there wasn't time, but hopefully people will preserve those discussions and questions, so we'll at least have a good hour to hour and 15 minutes with the panelists here from this morning to answer some questions.
The two sessions we have before lunch both have to do with regulatory. So for the first presentation --
DR. HERTZ: Sharon Hertz.
DR. KROENKE: -- no, I was going to get your announcement. I have the name -- who is division director of the Division of Anesthesia, Analgesia, and Addiction Products at the Center for Drug Evaluation and Research at the Office of Drug Evaluation for FDA in Silver Spring. And Sharon is going to talk about a regulatory perspective on opiate-sparing clinical trials and adcoms, and this will focus on drugs.

Presentation - Sharon Hertz

DR. HERTZ: I'm not going to talk about the regulatory aspects of this.

(Laugher.)

DR. HERTZ: It's just a handy placeholder because I'm always behind on getting things to the organizers. So sorry about that. I'm just going to share some thoughts about what comes up when we hear from sponsors who are interested in this and some of the things that we think about. We don't really have a formal -- well, we kind of have been providing advice, but we're working on a guidance. That's the big news. And it's going through clearance. So everybody in this room will have an opportunity to comment on this when it goes out for public comment. Yay! So you'll all be ready to provide us with the help we need to make this a better guidance by sending us comments to the docket.

A lot of this you've heard in great detail today. The critical questions really are why even bother sparing opioids? I know this may sound a

little heretical, but they're perfectly good analgesics. So why do we need to spare them? And there's a variety of reasons that we've heard. People are troubled by adverse events. You've got a lot of information on that. We worry about people overdosing, and we worry about people developing addiction.

What about the general societal concerns? This is always a challenging one for us because we have been legislated to taking societal concerns into our regulatory decisions, because until it was legislated, we never thought about anybody except the single patient involved.

So anyway, we worry about the overall benefit to patients. We look at it in the context of the greater picture of public health, and we know from a variety of surveys that the opioids that are being abused in the community, the prescription opioids, part of it, are often obtained ultimately from a physician, whether it's the patient or more commonly not the patient who ends up abusing the drug.

Here's the interesting thing. Perhaps some of you are already aware of that. But what does industry think, and how do we respond to these different proposals? I would say that the most common proposals we see involve the two dreaded words, "statistically significant," which really is helpful in terms of understanding what happens by chance, as you all well know, but may have very little relevance for an actual clinical outcome benefit.

So we've had everything from, simply, well, there's a difference in the amount that's being taken; let's look at it as a percent reduction. That's a great way to exaggerate a clinically meaningless difference.

(Laughter.)

DR. HERTZ: And let's look at the number of doses -- I actually have an interesting example for that -- and the percent of patients opioid free. And that's actually an interesting concept because when are they opioid free? Are they opioid free post-op, but then they go home with 600-milligram

oxycodone, or are they opioid free for their entire acute pain recovery? And then there's also more to worry about with chronic pain, which you've heard about.

So we often struggle with the concept of clinical meaningfulness. And this group has over the years struggled with trying to define clinically meaningful differences in a variety of settings, and it's really hard to do for all the reasons that we know about. It's all relative, and we always have to look at clinical meaningfulness in the context of benefit and risk.

So it's great if you can reduce the opioids but not if you lose your liver in the process. And I can spare opioids pretty easily by denying them to patients, which is apparently an all too common phenomenon these days, but that's not achieving the goal of managing a patient who has pain in a clinically responsible manner.

So these are some of the questions. How much of a reduction is important? And I dare say that we will never have an absolute number to

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answer that question, which is always what people want from us, are absolutes, because then they can target drug development more effectively and efficiently. And it would be great if we could come up with that, but I don't see that happening anytime soon.

What about the duration of use? That's another important characteristic; again, the adverse event effects. And what's it relative to? A reduction relative to what? And then the point that was also raised before is how do we look at pain intensity over the course of this process, and how much reduction in pain management is reasonable to expect patients to tolerate? Because frankly, we can reduce opioids a little, reduce opioid adverse events proportionally and increase pain proportionately. I'm not really sure that that's doing anyone a favor. Well, I am pretty sure that's not doing anyone a favor.

I'm giving you specifics where the information has already been made public. This was an interesting advisory committee, and these are

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two studies for Exparel, which is a liposomal bupivacaine product that's typically administered in the perioperative period. And here is some data from that. I'm not even going to say whether I think this is right or wrong.

These are the kinds of data we get, and these are the data that underlie some of our conversations about what is a valuable opioid-sparing outcome. Here we have an AUC for numerical rating scale or a VAS, visual analog scale, depending on the studies. We have two different doses in the two different studies. We have two different evaluation periods. The first study was a 48-hour period. The second was a 72-hour period.

We can see the AUC, some pain intensity difference in the first row. We can see the total amount of opioid use converted into morphine equivalence. This is obviously post-op. And there are two things that are quite different. In study 327, we have the active arm used, on average, 25 milligrams of morphine versus 113 in the placebo

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group. That sounds like a big difference. I think that might be meaningful, but I'm not sure how to tell. And I would need to have that conversation with people here.

Then in the other one, 93, 122, much harder to tell if that's worthwhile. And then, unfortunately, we don't have the last row for both substudies, but out of a study of 140 people, 9 on active versus 1 on placebo required no opioids during that 48-hour period. What does that mean? Is that opioid sparing in a clinically meaningful manner?

That's the question. I'm not answering any of my questions today.

(Laughter.)

DR. HERTZ: I'm only raising questions.

I don't know what's public on all of these, so I made this drug A. But the dosing might tip it off for some of you who have been following some of this. This was an interesting one because this wasn't our product. This is a product from another division that was treating a syndrome. We do

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actually believe in syndromes occasionally. Where is Nat? We do occasionally agree that there are syndromes.

But in this one, pain was one aspect of it, and they looked at the amount of opioids. And initially, this application converted the opioid use into morphine equivalence, except it was Percocet and codeine with Tylenol, oxycodone with Tylenol, and it wasn't even around-the-clock use.

So we had morphine equivalence of three, on average, which was a completely meaningless statistic for a patient population that used intermittent combination products over the course of the study period. And I think in some of this, there was also some tramadol, acetaminophen products, but they were all combination products, and they were all intermittent use.

So we decided that we would describe that and look at the number of tablets per month because, again, morphine equivalence seemed hardly useful in this setting. At baseline, you can see it was pretty balanced in the first row across two

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studies of two different doses of drug A plus placebo.

I like medians a lot in addition to means, so I always push for them because I think here it's very telling, especially when you look at the range. This was a pretty varied population. Some people were using 184 tablets per month at baseline. This was clearly not the same as the person using zero. And just averaging that together made absolutely no sense to me. It also shows it's fairly balanced at baseline.

Let's look at what happened at month 3. The higher dose of drug A dropped by an average of 5 tablets a month. Okay. That's good. The median went down to zero. Well, that's interesting, but the maximum actually went up for a couple of people and stayed fairly stable for those high-end people who were using more tablets per month.

Here's some more data from this. These are actually in the PI. I just don't know if it's gone public yet. I think the product was approved. Here we have the number and percent of patients on

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an opioid at baseline who went off the opioid at 3 months. So how many people no longer needed to use opioids on a regular basis?

Here, well, those are a little bit more interesting because it kind of tells us something other than these odd pill counts, which I think was useful. But here, we sort of see a difference. So we have a bigger number in the active groups than the placebo, but a fair number of the placebo patients went off their opioid as well, but then what's the converse?

How many people who started off not requiring opioids ended up on some opioids by the end of the study? Because there's this natural history to this process as well. And lo and behold, yeah, some people ended up going on who hadn't been on before, not as many who went off. And in the first study, there was a little bit of a difference, and in the second study, it was a little bit more.

So, I don't know. Is this drug opioid sparing? I think it would be more telling if we

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actually had pill counts in association with this as well. But if we go back to here, if on average the population reduces the number of pills per month by 3 or 8, I don't know. If you still have people using almost 200 pills over the course of a month, is that opioid sparing? I told you I wasn't going to answer any of that.

This drug was not approved. Here is some information. This drug product's whole reason for existing was presumably going to be a better adverse event profile than the two opioid comparators that were studied. Here are two studies. There was a low-dose study and a high-dose study. Here's the general adverse event profile, one of the things that Nat mentioned, as one way to consider looking. And you can kind of see things are a little higher, a little lower.

It doesn't look especially different, at least to me. The high dose, opioid 1, maybe looked the best in some things. It was less constipating, but, again, it was a low percentage, and the high dose study was much smaller. So I don't know.

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This overall doesn't look particularly informative as to opioid sparing, but it depends.

Then what about supplemental oxygen use because that's a big issue if you're having respiratory depression. This is post-op. That would be great to try and reduce the risk of post-op respiratory depression. And this table is kind of wacky because what we did was we kind of smushed things together because some studies had different dosing arms.

The gray boxes just show that, for instance, in study 1e, there was all high dose. And if you look at that, the supplemental oxygen use as one possible measure for a benefit didn't pan out. So is this the right measure? What if we looked at oxygen saturations? What's the trigger for using supplemental oxygen? Should we have looked at some other measure?

In the low-dose group, maybe, I don't know, it was just really hard to tell what -- it looks like my percentages are a little off on some of that. Anyway, this is the kind of thing that a

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study -- now, I have to say that there were many measures of evaluating respiratory depression in this study, and it did include things like pulse oximetry and a variety of things. And at the end of the day, this one didn't really show an effect. But this was one way of trying to evaluate it, and unfortunately for this sponsor, drug B didn't do what it hoped would happen.

That's why I have in terms of slides. I couldn't find some of the other studies that I was looking for last night. If you look at some of our labeling -- and I'm sorry that I didn't put these up -- we do have some information in labels about the amount of rescue opioid use. And we use it in a variety of different ways.

For instance, for pediatric analgesic studies, especially for the very young, we don't really use placebos. We use an add-on design. So the amount of opioid use is really the primary outcome measure. It could be adding an opioid to an opioid. It could be adding a non-opioid to an opioid. There are all kinds of combinations.

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For the parental acetaminophen and the parenteral ibuprofen, we have some information in there. Also, these were older programs, and they even have some information about the relative amount of opioid used in the studies in adults. It also says we don't know what it means because there were some differences. But that was all we had was numeric differences. We didn't have anything else to go with it. So we said what we knew, which is we don't know what this means.

That's an idea of some of the things that we're seeing. I can tell you that we generally have not favored some of the arguments about any statistical difference is meaningful. From a societal perspective, some people will say any reduction is useful. I'm not sure that we're ready to make decisions on a small reduction in opioid use for a product that really doesn't show any particular benefit to the patient that we can identify on a societal perspective. It's asking the patient to bear a lot of the burden because we're now adding another drug, and none of these

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are side-effect free.

So these are debates that are ongoing, discussions that are ongoing. And as I mentioned, we tried to capture some of this in guidance form, and I'm sure it is going to be amended based on input. When it posts, I'll try and get the link so that it can be sent out and you don't have to look around for it. And also, if you do want to provide us with some comments, it would be appreciated.

(Applause.)

DR. KROENKE: Actually, Sharon, let's see if there are some questions because you ended early, and we'll see if there are. You decided not to answer questions, but maybe the group will ask questions --

DR. HERTZ: So you should never end early --

DR. KROENKE: -- that force you to answer questions.

DR. HERTZ: -- is the lesson, so I will speak longer next time

(Laughter.)

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DR. KROENKE: That's why I'm keeping you at the microphone.

Any questions from a regulatory FDA standpoint or anything Sharon said?

DR. HERTZ: Nat, what is the question that you have?

DR. KATZ: If somebody did present you data that said the patients on study drug used this amount of opioid and the patient on placebo use that amount of opioid, and there was a difference, whatever their magnitude was and whatever the p-value was, how would you decide whether that difference was clinically important or not?

DR. HERTZ: Well, we're trying to have conversations early in development to ask people to provide some basis for us to make that decision ahead of time so that, A, the sponsor knows that's going to be the question; and B, we have something to go with that difference. So it depends how the sponsor has chosen to do that study and support why they think perhaps that is clinically meaningful.

DR. GAN: TJ Gan from Stony Brook.

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Sharon, I enjoyed your talk. I have a question that relates to clinical practice versus trial for regulatory purposes. There is no conflict between trying to take care of a patient in as best we can manner versus trying to have a new drug approved because I think those two are in conflict in that if you want to provide the best care for a patient, we know that multimodal works well, and we're trying to use that model to take care of patients. At the same time, we know that if you use that model, it's very difficult to assess what is the effect of a particular drug.

Again, I don't have an answer. I don't know whether -- how do you go about reconciling between clinical standard of care versus trying to get a drug approved, understanding there's a hurdle to trying to demonstrate something if you are using more closely the clinical trial in a standard-of-care manner?

DR. HERTZ: That's a really good question, and there's a lot that could be said about that. Let's see. You're exactly right that the use of a

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product in practice is often not the same as the use of the product in a clinical trial that was intended to demonstrate efficacy and safety for the purpose of a regulatory decision. There are a couple of reasons why that is, that I know about, and I'm sure there are other reasons out there as well.

We need to understand that the drug does what the sponsor says it does. If it's an analgesic, it needs to lower pain intensity, and it should do so without dramatically worsening function and global, so we often look at those.

Does an analgesic have to improve function? That's a question. Does it have to do something other than lessen pain and not have side effects that are so severe to make that benefit unbalanced, an unfavorable balance there. I'm going to look at the transcript for this and squirm over these answers.

So let's assume the adverse event profile is not particularly bad for an analgesic, and it lessens pain, and it doesn't seem to worsen other

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aspects. It could meet the regulatory standard. Is that the best way to use the drug? Probably not if it's an analgesic. So could it be studied in a more clinically relevant setting? Now, I didn't say should; I said could. Should is for you guys to think about. Could is what I think about. And the answer is sure, it can, but it's harder. Right?

So one could develop or adopt a standard multimodal protocol that's been used successfully in an institution and use the study drug -- use all that as stable background, and then have the study drug be the variable.

So if the multimodal approach is to take somebody following -- let's say it's a big surgical procedure like a knee. There's going to be a lot of things done. They're going to get a block. They're going to get maybe -- I don't know. Some places are routinely using gabapentinoid pre-op, perioperatively. Some may or may not believe in NSAIDs in that setting depending on your thoughts

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about Cox-2 and healing.

So there's all that going on. And then there's going to be an opioid because if you want the patient to come back and let you do their hip, you're going to have to give them some opioid for their knee. Right?

So let's say you now have drug C. What class is it? Is it to replace one of the existing parts of that multimodal therapy so you can use that as your variable? Is it an addition to that to reduce the need for some of these others that have adverse events, so then that's your variable?

So you can have a placebo-controlled study with a background of this other therapy. Unfortunately, if you manage your patient's pain very effectively perioperatively by using a standard multimodal approach that works, your assay sensitivity goes away down, and you need a much bigger study. Well, I'm in favor of that because then I know how the product works in a much more real-world setting. And we're all about real world these days and real-world evidence, and that would

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be terrific.
Now, if you guys could convince the companies that you consult for to do that, great. But is that really the way to get new products, especially potentially better products to market, to burden them with a requirement that potentially means more money, bigger studies, harder evidence, you know, burden? I'm not sure that we're doing anyone a favor, but you could argue that we're not doing anyone a favor by not requiring it, so I don't know. But that's sort of the reality of where we are.
I think that another option could be to have the more limited study premarketing, get your product on the market, and then start really looking for some big claims. Look at how fabulous we are in this setting of multimodal, much better than this other product, and then you can get some postmarketing studies, and that would be great. We just don't tend to see those.
So there are many ways to look at that, but it's hard for me to, -- I think that there are many

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ways to approach this. So the bottom line is -- and of course we're talking about acute pain right now, but it holds true for other settings -- should have chronic pain drug be studied in the absence of all the things we don't allow people to do typically in clinical study?
So if we're lucky, the anticonvulsant or antiepileptic that's been stable for 3 months is allowed to continue, and maybe sometimes physical therapy or some other complementary therapy, if it's stable, is allowed to continue. But typically, those are not parts of the clinical study.
So the chronic pain drug may also be studied in a more narrow manner than ideal chronic pain management would prefer. But then it's up to you folks to integrate it into that, assuming you ever get coverage from your patients' insurers for any of that. That's a whole another story.
Did I use up my time?
DR. KROENKE: No, no. That's good.
DR. HERTZ: No more questions. Okay.

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DR. KROENKE: There may be more questions at lunch [inaudible - off mic].
Excellent. Our final presentation before lunch will be by Carlos Pena, who's the director at the Division of Neurologic and Physical Medicine Devices, Office of Device Evaluation at the FDA in Silver Spring as well; and he'll be talking about opiate-sparing clinical trials and objectives related to devices.
Presentation - Carlos Pena
DR. PENA: Good morning. I always get nervous when FDA's before a lunch session. The FDA barring people from getting food is not the branding that I was hoping we would go out with.
Devices are an up and coming technology sector that I think it's worthwhile to spend a little bit of time with you on, introducing you to medical device regulation, and specifically three parts of this presentation, including introducing you to that regulation. The second part is some factors to consider in what we look for in evaluating devices, and the third is the best ways

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to engage. I'm not familiar with a lot of you, and I'm hoping that we can change that.
So our vision at Center for Devices and Radiological Health is that patients in the U.S. have access to high-quality safe and effective medical devices. Public health importance is first in the world, and we take that pretty seriously. I'm going to show you some data that speaks to supporting that vision, and our primary interest is getting products to patients.
First off, what is a medical device? A medical device is defined as an instrument, apparatus, implements, and it goes on and on and on. So you might be saying, Carlos, there are several provisos, some addendums, a couple clarifications; what is a medical device? If a diagnosis treats or prevents a disease in a manner other than through chemical action, it may be a medical device. And one can classify a device as a medical device, even in the absence of claims, when it impacts the structure of function of the human body.

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We classify our devices into three classifications, class 1, 2, and 3, with regulatory oversight increasing from class 1 to class 3. And the device classification regulation defines the requirements for any given device. For example, most class 1 devices are exempt from submitting an application to FDA; most class 2 devices are what's called premarket notification or 510(k); and most class 3 devices require premarket approval. They're PMAs, and we provide oversight across these three classes using tools known as general and special controls, which help to communicate to the sponsors what they need to do to get their product to market.

As mentioned on the last line, medical devices can be classified into three classifications, two of which are highlighted here, class 3 and class 2. These are the higher risk classifications. For example, we receive several dozen PMAs or class 3 devices each year. These are the highest risks and require clinical data, typically.

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A second pathway is a 510(k) submission pathway, so there's something already on the market for which these products compare themselves to. We receive several thousand 510(k)s each year. They may contain clinical data, but typically they do not. And finally, a third regulatory pathway is the de novo submission process, which includes devices that aren't comparable to anything on the market and present a lower risk than other types of devices. Once they have been granted to enter the marketplace, they then serve as a predicate to subsequent devices that move along the 510(k) pathway, class 2.

So when is clinical data needed? And this often comes up in the device realm. Typically for PMAs, clinical data is needed. For de novo submissions, clinical data may be needed but may not always be needed. And 510(k) submissions, clinical data is typically not needed, although there are cases where clinical data was submitted.

So you're again saying, Carlos, okay, there's a lot of provisos here, addendums. When and how do we find out if clinical data is really needed for our submissions? And my response to you is that you can request feedback through the presubmission process through our center before hopefully starting your study. And I'm going to return to that about how to engage the Center for Devices. The presubmission process is a free process, and hopefully people use that process to engage us before they begin studies, which can be expensive.

Here's a favorite slide of mine. We've been engaged in the neurotechnology sector for some time. Here I show you an array of products beginning with neurothrombectomy devices on the left-hand side, epilepsy, and ADHD diagnostic, prosthetic arm, migraine, device, and microcatheters for the neurovasculature. The goal is not to discuss individual data sets with you for each device, but share with you here that each device went through a regulatory pathway that was, in part, tailored to the individual risks and benefit profile of the device. And when other

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products are targeted that may involve different product areas across the agency, we work with our colleagues, such as Sharon and her staff, to coordinate our reviews.

First I'd like to share with you how serious you are about standing up clinical studies that evaluate devices. The faster you can stand them up, the faster you can evaluate the data. And the faster you can come out with the data, the faster you can submit an application to us.

Here I show you decreasing timelines over the past several years where in FY11, it took approximately 400-plus days to reach a full approval of an IDE study. IDE is investigational device exemption, a clinical study that we use to evaluate medical devices. FY13, we dropped that by half, and '14, '15, '16, and '17 is late data. That is now down to 30 days, the median time to full approval.

That's a pretty striking drop. We take safety very seriously, but we would like to start these studies as quickly as possible with safety

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being a focus of our reviews, but standing up the studies is a priority for us, and that's come at a cost in our space. We are trying to look at how we can make this sustainable. But we are very serious about standing up these medical device studies, including pain, substance-abuse disorders, and other related conditions.

The take-home message here is that we want to accelerate getting these products to market, and the fastest way is we can work with you on getting these studies up and running within 30 days.

Another way we are successful in meeting those timelines is through guidance. Here are several guidance documents for medical devices that are relevant to neurological products: presubmission guidance, early feasibility, clinical studies guidance document, pivotal studies, and expedited access. These guidances help to clarify to sponsors how we evaluate medical products. A little bit different than the drug side of the agency, in the medical device side, we have what's called typically a feasibility study, and then we

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have a pivotal study. So we base our marketing decisions typically on that pivotal study.

A few medical device concepts that I think come up in this realm as well include the classification; valid scientific evidence, which I'll come back to; benefit-risk; reasonable assurance of safety and effectiveness; and least burdensome means, as well as indications for use.

I attended conferences actually yesterday on the west coast. I was in the meeting and walking down the exhibitor booths, and someone comes up and says, "Hey. Can you approve this device?"

(Laughter.)

DR. PENA: And I'm looking at that list, and the questions that we need to ask in the device realm, which are comparable in the drug realm, is that there are a lot of factors that we need to take into consideration. And we weigh all of these factors almost in a tailor-made approach. So it's never an easy question, but I am assured that the device questions that we do ask help to get the right products to the marketplace.

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Valid scientific evidence is a factor that we use in our medical device reviews. We look at well-controlled investigations, to partially-controlled studies, to reports of significant human experience. This is a little bit different in our regs than the drug side, but there are times where products, based upon those factors in the prior slide, the valid scientific evidence from those studies would make sense to consider moving that product to the marketplace, but it requires us to delve into the data that is submitted to the agency.

A few regulatory issues that I wanted to just maybe touch upon, on the diagnostic side, there are a few factors that I thought would be important to highlight. One is the need for a scientific consensus on the diagnostic criteria for any given disorder using best-estimate diagnostics, blinded assessors. I do not recommend using the same data set to both develop a diagnostic or biomarker, and validate that same data set with the same population.

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On the therapeutic side, there are other issues, that we also look at medical device development, including the trial design; use of control arms in the study; use of a sham control, active versus inactive; and the blinding assessments. Many of our products can be neuromodulatory, so we are interested in, based upon the factors that I've mentioned, how the blinding was assessed.

Clinical outcomes is a factor as well. I don't believe we are against any particular endpoints, whether they're tried and true, or they may be even novel, so long as there is an adequate justification and rationale behind any given endpoint for a medical device study. We also want these studies to be generalizable, and the information from these studies informative to the end users. We also look at the safety side of device development such that we look at all adverse events at the time of consent with preferably, depending upon the type of study, the type of device, independent adjudication.

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So I think the last couple of slides here are meant to impart that we have parallels and different product reviews in the agency, but device is also very much interested in the safety and effectiveness of products that reach the marketplace.

A couple activities and initiatives that we're working on at the center, one is the focus on patients, using patient and preference information; partnering with patients. We often meet with advocacy, clinical organizations to make sure we match our expectations and match our awareness to different patient groups during the device development in our review. We have guidance on, on that.

We have a mobile medical applications guidance, which I think is presenting some unique opportunities for device development specifically in the pain area, and we have guidance that takes a risk-based approach for using mobile medical application technology, whether it's diagnostic or therapeutic.

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We also have real-world evidence activities and initiatives. This is an interesting data set where there's a lot of data collected, and not necessarily in a trial design model, but we are looking to evaluate the ways for which large data sets, depending upon the indication, can be used and leveraged to support regulatory decision-making. So we have some guidance on that as well.

Just to close out some of the organizational points that are in our center for devices, on the right-hand side, you have the Office of Device Evaluation, and that is where the lion share of the premarket review occurs. Within ODE or device evaluation, there are seven divisions, one of which is the Division of Neurological and Physical Medicine Devices.

We currently have five branches, and many of the pain and substance-abuse disorders would fall into the psychiatry branch, although sometimes we have submissions crossing both psychiatry and neurological in the neurostimulation devices area,

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and also neuro-diagnostics also plays a role in pain assessment and some of the other diagnostic devices that we have.

The best way to engage the center is through the presubmission process. It's a free opportunity for us to get to know your product area. And many times, the presubmissions can even include informational submissions, whereby folks introduce us to their devices, and we can map out the regulatory landscape for those products early on.

If people think it's too early to contact us, that's probably the best time to contact us, because it can be very expensive. It would be a missed opportunity if you are involved in device development. You do your study. You have all the results packaged up and ready to go, and we're not on the same page with regard to the outcomes, or the results, or the methodology that was used. There's a lot of information available, recent article in Neuron. We also have a website for the neuro and physical medicine devices division. And we have had a number of webinars online that map

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out the different regulatory pathways for products in this area.

In closing, I think there's a lot of opportunity for the device area to also play a role in some of these disorders, some of these conditions. We are getting into this space with different products and diagnostics. And we hope that folks contact us early because we want to make sure we're on the same page at the end of the road and bring product areas to conclusion in a positive way.

One last note is that there's an FDA innovation challenge where we've made a call for medical devices to prevent and treat opioid-use disorder, which includes digital health and diagnostic devices. You obtain breakthrough device designation, which allows for more of an investment in the interaction that we have with sponsors and developers to help those products get to the marketplace, and those submissions are due September 30th.

I'm also accompanied by two individuals from

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the Center for Devices, Dr. Jonathan Jarow and Dr. Allen Chiu. We're sort of all along the back wall there, evaluating all of you and the questions there. But if you get a chance, it would be great to make some contacts. I think we want to have a good start to this technology piece of the puzzle and make sure that it is successful.

Just in case, if you haven't taken anything away from my talk -- and if you're focusing on dry cleaning or what you're doing at lunch time -- I'm giving you my contact information. Sometimes I hear a lot of you, I don't know who to contact at FDA. Where do I start with devices? There's my email address. I think you'll be surprised about the contact that we have and the interaction we can have with device development. Thank you.

(Applause.)

DR. KROENKE: We have about five minutes before we close. Question? Yes?

DR. FARRAR: A very interesting talk. One of the questions that always comes up, if we take a potentially opioid-sparing process, like a spinal

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cord stimulator perhaps or nerve stimulator, there are spinal cord stimulators that you can put in temporarily and remove, and they're ones that -- sorry. John Farrar, University of Pennsylvania. I forgot about the recording. And there are spinal cord stimulators that require an open procedure to do.

So I come to you with a new device, where I'm going to plaster your entire spine. I'm going to just open you up and put something from guzzled to zatch. And I show you that it's as safe as anything else. I guess what I'm getting at is how is the decision made not only about the device in terms of its functioning and so on, but ultimately the risk of insertion, or the risk of use, and then ultimately the potential benefit relative to other devices that work in the same space?

I understand that's a very complicated issue, but I just wondered what --

DR. PENA: That's the questioning of the conference all the time. There are a lot of points there to unravel. One is the invasiveness of the

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product. One is how do you assess the benefit? What is the benefit, purported benefit? One is where is the patient at in the continuum of treatment? One is where do we have prior evidence of the product and what is the prior clinical studies available? How are benefits characterized and by what measures? Are these clinicians or patients?

If you have a data set, how robust that data set is? Is there some uncertainty in that or not? And is there a least burdensome way, if there is a robust effect, of getting that to the marketplace? How should we work together to really expedite that least burdensome to the marketplace?

Those are all the types of things that we would walk through and try to look at the totality of the evidence in making a decision. If those are all in place, there's a high degree of benefits, there's a low degree of uncertainty, there's a low degree of risk or the risk has been mitigated through labeling or other experience, when those things line up and we've talked about that in a

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presubmission before you've done a study, we're in a good place I think.

When those things have not been discussed and we have uncertainty about the beneficial impact of those that have been treated versus the control group that have gotten standard of care that are doing probably maybe better, when those uncertainties start to add up, that sort of shifts the ratio of the benefit-risk, the decision process that we make in devices.

So I don't really have a yes or no answer would we go forward with that. I have the factors that we would need to think through, that my clinicians, that my scientists, that my engineers would need to walk through in a review team to make the best decision of whether to stand that study up in an IDE study or to make a decision of getting that to the marketplace. It's a great question.

DR. KROENKE: A question there?

DR. FIELDS: Howard Fields, UC San Francisco. How good was your postmarketing follow-up for devices? Are there requirements to

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keep patient records? How would that be done?
DR. PENA: Right. For premarket studies, we may require 12 months of safety and effectiveness data, depending upon the invasiveness of a device, during the clinical phase of product development before that is marketed. That will give us a piece of the puzzle about what we can expect long term.
Then there's also postmarket surveillance that we have. Office of Surveillance and Biometrics looks at safety signals. We don't know the denominator, but they review reports of these signals that may come in through our databases, through voluntary reports about different products. That's another method, that we are evaluating different products in the marketplace.
In some cases, when you talk about class 3 devices, like I mentioned at the beginning of the talk, there may also be post-approval study requirements or post-approval studies that need to be performed over more than one year, 3 years, 5 years. That depends, again, upon these types of factors that we need to walk through at the time of

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a marketing decision. But it would be measured. It would be a proportional type of oversight in the postmarket space.
The other thing that we're evaluating is how to combine our premarket review and postmarket surveillance into one team effort, and I think we're looking at ways to organize our center so that there is one office that could perhaps look at pre- and postmarket issues with sponsors. And the sponsors would get a lay of the landscape at one time for their product.
DR. FIELDS: Would that information be available to the public if you have it?
DR. PENA: What is that?
DR. FIELDS: Would that information be available to the public?
DR. PENA: Definitely.
DR. FIELDS: Okay.
DR. PENA: There's been some discussion at AdvaMed type conferences about this new organization at the Center for Devices.
DR. KROENKE: One more question, and we'll

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be taking a lot more during our working lunch. Yes?
DR. OSHINSKY: Michael Oshinsky from the NIH. I have a question about 510(k) clearance and its perspective -- either from the physician's perspective or from the patient's perspective, of what kind of clearance or approval you're actually giving on the devices. In my experience from the physician's perspective and the patient's perspective, when the FDA gives 510(k) clearance that they're giving clearance for the efficacy of the device. And it's not my understanding that that is included in the evaluation of them at that stage.
Is that correct?
DR. PENA: I think the 510(k) clearance process includes both safety and effectiveness. There's a reasonable assurance that that product that's being cleared under the 510(k) process is equivalent to a predicate product that's already on the market that has established safety and effectiveness.

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DR. OSHINSKY: I got that. So the equivalency is only -- when you put up the slide, you said that there wasn't data in humans that was required for the 510(k) clearance.
DR. PENA: Right. I said may not be included in a 510(k). I have my notes here.
DR. OSHINSKY: Yes. No, I've got it.
DR. PENA: So in a 510(k) clearance, typically clinical data is not included because you already have products on the marketplace already as predicate devices. But in some cases, there may be some 510(k) situations where clinical data is included. In those situations, we'd love to have a presubmission discussion with the sponsor to make sure that they know that clinical data should be part of that application before a marketing decision is made.
DR. OSHINSKY: So you're saying that 510(k) clearance includes efficacy studies.
DR. PENA: It may include efficacy studies, depending upon what device you're looking at.
DR. OSHINSKY: So that's exactly the point

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I'm getting at, is the confusion from the patients or the physicians' perspective of what evidence was used for the FDA to make that 510(k) clearance designation so that they don't know what to communicate either to the patients or for the patients to understand what they're using.

DR. PENA: So let me just answer that, and maybe Jonathan Jarow would like to take a swing at this too. But the 510(k) decisions include a summary of safety and effectiveness. In that summary there is information about what the evidence that was included in that submission came with that application. That as a safety would be a good source for information for physicians to convey to the patients if that's a need.

Jonathan, do you want to do anything further?

DR. JAROW: It's not an exact analogy, but the 510(k) process could be compared to generic drugs. And when we approve generic drugs for marketing, we do not require clinical evidence that these drugs are safe and effective for their

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intended use. We require that they show bioequivalence to a reference-listed drug.

This process is very much similar to that. So if there is a predicate device that's marketed, that's been found to have reasonable assurance of safety and effectiveness, and this device has been shown with bench testing and other testing to be within all the same parameters, so very much like bioequivalence, you can get to market without any clinical data whatsoever.

However, if they're outside of those parameters in any way, shape, or form, it may be in order to demonstrate substantial equivalence that clinical data are required.

DR. PENA: Right.

DR. JAROW: So some of the special controls for class 2 devices actually require clinical data --

DR. PENA: Exactly.

DR. JAROW: -- with each new device.

DR. PENA: A good example is neurothrombectomy devices. Those require clinical

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studies as part of their clearance in the 510(k) paradigm.

DR. KROENKE: Thank you.

(Applause.)

DR. KROENKE: What's really good is nobody fell asleep before lunch, but we're getting more feisty. So that's a good sign for our discussion.

(Laughter.)

DR. KROENKE: There are a lot of hands that went up during the morning presentations. I hope you've remembered your question, and your memory's not dulled by feeding yourselves.

I think what we said is we're going to have lunch and then rejoin here, do you think a 12:15 or 12:30?

So 12:15, whoever's here, we're going to start discussing. If you're not quite finished, you can bring your lunch to this room, but you'll have nearly 45 minutes to lunch next-door. We'll rejoin here at 12:15. Thanks.

I do want all the panelists at that time to come up to the table for lunch, so everybody who

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spoke this morning needs to be at the table at 12:15.

(Whereupon, at 11:35 a.m., a lunch recess was taken.)

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A F T E R N O O N S E S S I O N
(12:20 p.m.)
DR. KROENKE: As we get started here, we're going to have a couple minutes, up to 3 to 5 minutes, for updates from Michael Oshinsky from NIH and Jeremy. Everybody has been hearing about this -- I'll use the short term, the "pain moonshot," -- well, they did it for cancer, so this is important; so this extra money over the next several years, targeted to the kinds of things that people are interested in.
Michael?
Presentation - Michael Oshinsky
DR. OSHINSKY: Thank you very much. We're going to be really short, Jeremy and I. I just wanted to introduce the programs and the planning that we're at, at this stage, for the HEAL Initiative, which is helping to end addiction long term.
My name is Michael Oshinsky. I'm the program director for pain and migraine at the NINDS, which is one of the institutes at NIH.

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There's a whole suite of programs that are going to be coming for this money. You heard it several times, this $500 million being bantered around. This $500 million is really for three different components. One is for pain, the other is for opioid-use disorder, and the other is for reversing overdose. There are three components for this, and they're three distinct ones. $250 million has been reserved for dealing with opioid-use disorder and for reversing overdose and $250 million for pain.
The plans we have at this point for pain -- and I'm going to speak about a few of them, and Jeremy's going to mention a few -- one of them is to discover new non-addictive targets and validate them for treating pain. The second is to develop a platform screening program in animals similar to the epilepsy screening program that's been going on at NINDS and funded by them for the last 40 years. Then another is to discover and validate biomarkers for pain treatment or for clinical trials or outcome measures.
So those are some of the programs that are

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ongoing. If you go to the NIH HEAL website, H-E-A-L, you can see the current funding announcements that are available and which ones through notices will be coming soon. So please keep going back to that website, and there's a way to register on there for you to get updates, to put your email address in.
Now, I'm going to pass it over to Jeremy to tell you about some of the clinical programs.
Presentation - Jeremy Brown
DR. J. BROWN: Thank you, Mike, and good afternoon. My name is Jeremy Brown. I also work at the National Institute for Neurological Disorders and Stroke. I wear several hats there. One is that I am helping to put together this clinical trials network for pain. That is a clinical partner, if you'd like, to the basics and discovery aspects of the HEAL Initiative. We are focused on bringing to clinical trials some -- we'll call them assets, and they're drugs or devices that have not progressed perhaps past the phase 1 trials and are perhaps good compounds,

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good assets, but for one reason or another didn't proceed further.
So we're interested in the public-private partnership to help to bring those assets into the phase 2 workspace and into the phase 2 research space, and that's going to be the main focus of the clinical trial network for pain.
We will also be looking into the comparative effectiveness space, and NIH will be funding, we hope, studies and compare it to effectiveness, perhaps looking at two different drugs for the same condition to figure out which one of them may be better in a head-to-head kind of way.
Much of this are moving parts that we ourselves are not fully aware of, and I think the reasons are very straightforward. Look, half a billion dollars is a lot of taxpayer money, and to give out half a billion dollars, you have to be pretty damn sure you're doing it the right way. So while proposals come up from Mike and myself, and many other people at NIH, they're really vetted and screened and making sure that we're really doing

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this in the most fiscally responsible way and in the way that's really going to get the most benefit to the patients out there.

So that's one of the hats I wear. I will just also mention -- and it's important in this audience -- I'm an emergency physician by training. In fact, I spent 15 years at George Washington University just down the road from here. And if any of you decide to go on a segway tour this afternoon and fall of your segways, and come up with a Colles fracture at GW, which was a pretty standard thing that we would treat this time of the year, I would have been a face that you would have seen happily injecting you with some IV dilaudid to help treat your pain while we set your Colles fracture.

(Laughter.)

DR. J. BROWN: So I'm interested in the opioid space as well. NINDS is not in that space directly. That is really the mission of NIDA, the National Institute on Drug Abuse. But the opioid space is an equal space, is an equal target, if you

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like, for this helping to end addiction long term. And there will be many programs in that space, in the opioid addiction space, including medically assisted therapy, looking at the best ways for doing that. Much of that, of course, happens in the emergency department setting, but much of it happens elsewhere in clinics that many of you may run.

So there are those two sides of it. We're happy to take a few very, very limited questions right now because we don't want to take away from, really, what the main focus is. I'll be here tomorrow to answer any more questions. We're both very easy to find online. Jeremy.Brown@nih.gov is my email. I'm happy to answer any questions that come up or just shoot me an email. Thank you.

DR. KROENKE: Maybe we can take a couple of questions. My guess is there are either no questions or there are many questions. But if there are a couple of questions, we'll be happy to entertain, and then we'll move on.

Any questions at all? Yes?

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DR. HAYTHORNTHWAITE: Can you tell us what the timeline is for the Clinical Trials Network RFA? Sorry. That was Jennifer Haythornthwaite.

DR. KROENKE: Since I said, everybody who's going to speak today will turn the microphone on and say who you are and where you're from. That's for the transcriptionist. So start over.

DR. HAYTHORNTHWAITE: That was Jennifer Haythornthwaite at Johns Hopkins University, and the question was about when the RFA is coming out for the Clinical Trials Network.

DR. J. BROWN: Thank you. So there is indeed a notice of intent to publish, which means that we're thinking about putting an RFA out. Actually, I can tell you that at least 4 RFAs have been written. I know because I wrote them. And they have gone through various stages of vetting and review, and they are currently waiting for NIH leadership, and then ultimately the HHS leadership, to approve these and make sure that they fit with the overall strategic plan and mission of the HEAL Initiative, and then we'll put them out.

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We've had various target dates that we have tried to meet, and for one reason or another, we didn't meet them. And we know this is frustrating to you. And more importantly, every month that we're waiting, 62,000 people a year, you divide that by 12; how many is that a month, right? And then you think if we could move the needle by 3 percent, that's a lot of people who are dying every month because we haven't started some of these programs yet.

So we're aware of it, and as soon as we can get them out. But they're written and ready to go.

DR. DWORKIN: I'm Bob Dworkin. I'll ask a follow-up question to Jennifer's. Is it correct to assume that given the delay in posting the RFAs, that the submission date that's now online of September will be moved forward?

(Laughter.)

DR. J. BROWN: Thank you for pointing that out. I should have gone back and corrected that. You're absolutely right. Just so that you know, our initial plan was to get this money out in FY18.

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FY18 ends at the end of September. So that was a very ambitious date. We knew we couldn't meet it, but then we wanted to get this money out in calendar year 18 ending in December. That was also a very ambitious date. We realize that those dates are now not -- we're not going to reach them, but we really are working very, very diligently.

Yes, I know I'm from the government and I'm telling you that we're working diligently.

(Laughter.)

DR. J. BROWN: But we really are, and we're just waiting for people with more wisdom than us to give us the approval. But that does need to be corrected. Thank you.

Working Lunch and Group Discussion

DR. KROENKE: Jeremy said at least he'll be around, and Michael maybe. But they'll be around yet during this meeting, so please curbside them if desired. And we also have long discussions tomorrow; it may come up. I really appreciate their attendance because this will be a very important source of funding for this area we're all

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interested in.

So having said that, it's going to be now open for an hour for discussion and questions. Believe me, if nobody has any questions, a few of the people here do have questions, but I'd rather start with questions from the audience. I know there's at least 10 hands that went up this morning that I wasn't able to recognize, so let's start. And since I don't know people's names, I'm going to do a lot of pointing. So again, turn the mic on, say your name, and ask your question.

DR. GROL-PROKOPCZYK: I'm Hanna Grol-Prokopczyk at the University of Buffalo. So a lot of the morning talks were about defining opioid sparing, and I really liked Nat's talk for trying to get very concrete about that and also about defining or conceptualizing some other things like opioid related adverse events.

This is maybe a terminological critique, but hopefully one not so petty as talking about commas and hyphens. Nat, your definition of opioid sparing seemed to essentially be reduction of

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opioid related adverse events. And it seems to me that that's sort of analogous to calling something a weight loss drug when it doesn't cause weight loss, but it simply reduces the negative effects of excess weight. So I just wonder if there are sort of two different things, there's reduction of opioids and there's reduction of the negative consequences of opioids, and maybe those deserve different terms to describe them.

Then a second question having to do with conceptualizations or definitions was whether it's worth discussing what we mean by maintaining pain control because you kept saying that it goes without saying that we want to reduce these adverse outcomes while maintaining pain control. And as TJ's talk showed graphically, patients may be very willing to make these cost benefit analyses where they're willing to give up a certain amount of pain reduction in exchange for reduction in those side effects.

So what do we mean by maintaining pain control? What if the side effects go way down and

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the pain control gets a little bit worse? But what if that's still something that patients would prefer? Is that then disqualified as a successful example is of opioid sparing?

DR. KROENKE: And just to comment -- because this will frame, and I think you did that. So the degree to which people have a question, they may initially target to some member of the panel, that's a good thing because otherwise, panels are going to look at each other quizzically and say who's going to answer that, and then sometimes every panel will have that person. And if the other panelists have a further comment about it that's contributing, fine, but we'll try to make sure every question doesn't have every panelist's comment on it.

But that's a very rich question, so, Nat, I presume you want to start because she mentioned you by name.

DR. KATZ: She did do that. In terms of the first suggestion, should we draw a conceptual distinction between the amount of opioids consumed

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and the consequences to the patient of a change in the amount of opioids that they've consumed, and presumably at this meeting a reduction because we're talking about reduction, I kind of like that idea, honestly. And maybe it would be clarifying to try to not combine them into the same concept but make them into different concepts.

I think Sharon already alluded to a way of thinking where first you figure out if the consumption went down or not. And then once you've done that, you ask the next question, which is, well, did that actually matter to the patient or can we even know whether it mattered to the patient.

So I kind of like that. It probably shouldn't be too hard to figure out words for these things, right? Amount of opioid consumed and the clinical consequences of that, something like that. I like that.

The second one was about these kind of -- I don't want to call them ambiguous, but the interpretation of composites, where you're trying

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to see, gee, your pain went up by some amount but your side effects went down by some amount. How do we determine whether you're better overall, and would we have tolerance for those kind of more difficult to interpret scenarios.

So if your opioid consumption goes down and your pain is better, and your opioid side effects are improved, then that's unambiguous. I know that you're better. If your side effects go down and your pain goes up, now I've got work to do to figure out if you're better, or worse, or the same.

So conceptually, I like what you're saying, that there are actually combinations where somebody could be overall better off even though their pain is a little worse or vice versa. So from a clinical perspective, when you see patients, you know that that's true from a clinical -- I'm always thinking about, well, how do you demonstrate it in a clinical trial?

In terms of demonstrating that in a clinical trial, boy, that is very hard work. You'd have to do a lot to -- it might sound easy. It's not easy

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because having published several papers on trying to come up with methods of computing and validating composite response indices, including ones just require looking at benefit or the ones where you're actually combining safety and efficacy, it's actually hard work. But conceptually, I'm totally on board.

DR. GROL-PROKOPCZYK: Jen said something earlier about -- what are they called? Door procedures? I guess there are things that could be discussed for how you would operationalize that.

DR. HERTZ: I guess my question is -- because remember, I'm not answering anything today. I'm just going to ask more questions.

MALE VOICE: Is your name Sharon Hertz?

DR. HERTZ: The new Sharon.

DR. KROENKE: Sharon Hertz from FDA.

DR. HERTZ: Oh, thank you.

MALE VOICE: And it's not a question.

(Laughter.)

DR. HERTZ: Janet knows me.

Why would you enroll somebody in a clinical

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study, separate from practice, at a level of pain management, and a level of analgesic, and a level of analgesic adverse events that hasn't already been optimized? So if somebody is willing to give up some analgesic effect to lessen side effects, shouldn't that be the baseline in which they go into the study? Because otherwise, it's a confound. The sparing effect is now confounded with the fact that they didn't need so much opioid.

So I think it's a bad place to start a clinical study because is the benefit attributable to the drug or just to less opioid, and you could have achieved that without the drug. So it becomes very challenging if that's how you start. The baseline has to be a little cleaner, I think, in order to separate out the effect of the drug versus the effect of simply reducing opioids.

DR. KROENKE: I'll just make a comment; I think a couple, which was mentioned, this morning. And I'm not going to talk about the perfect trial that goes to the FDA. I'm going to talk about a clinical thing. But one thing that was raised this

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morning and it keeps coming back is pain benefit versus adverse effects of the pain treatment. Even if we make each of those composite measures, like a composite bad scale, like these are all the bad things that can happen and here's your total score, which is probably more useful than a individual adverse symptom checklist, it also has a value of one outcome in trials rather than 12 in multiple hypothesis testing. It has to be relevant, though.

I also think it's intriguing to come up with a question that balances it. And this is not psychometric; I'm just making it up on the fly. But wouldn't it be a wonderful world to ask a single question, during and at the end of the trial, given your current level of pain and any side effects you might have had from the treatment, what's the likelihood you would want to continue this treatment? And you could ask that. Again, I'm making this up.

But I do think of this concept, why don't we incorporate the patient into an assessment of pros and cons, at least the secondary outcome?

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DR. KATZ: Yes, that has been done. Some of you may remember Janssen funded the development of an instrument called the PADT. I forget what it stands for, but it was designed to evaluate opioid -- it was designed to be a measure clinicians could use in practice when they're assessing the benefits and harms of opioid therapy, and they're real patients.

We asked about benefits, and we asked about harms, and then at the end, there was an item exactly like that, considering all the benefits, do you think that they outweigh any side effects you're having or something like that. So that instrument exists and data was collected with that, but we never actually looked at the performance of that particular instrument. That could be done with available data, I think.

DR. KROENKE: A lot of other questions. Way in the back, gentlemen? Yes?

DR. SIMON: Simon from Boston. In that context, I was wondering of the instruments that were presented this morning -- we saw some for

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acute pain and some alluded to chronic pain -- how many of those instruments were actually developed with patient involvement in each of the questions determining the utility of the question, the understanding of the question, and the impact of the clinical relevance to the patient?

Was this done with patients or was this done in the context of what we think that we know better what a patient really cares about?

DR. KATZ: I can answer that with respect to the instrument that I showed, which was developed for acute pain, and then, TJ, it would be good to hear you answer the same question with respect to the instruments you presented.

In the one that we presented, it was a soup-to-nuts, right out-of-the-box scale development program, so patients were involved every step of the way. There were I think maybe something like 300 patients involved by the time we were done, a multiplicity of different kinds of surgeries balanced with respect to gender and age and all the things that you would expect; bias

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carefully looked at, at the end, to make sure the different subgroups didn't respond differently and patients are involved in every step of the way in terms of item evaluation, item reduction, all that kind of thing.

So in that particular instrument, yes, but that was only validated for acute pain.

TJ?

DR. GAN: So I presented a few. One of them is the opioid related symptom distress score, the SDS, which I mentioned earlier was initially developed by Russ Portenoy for chronic pain. And we changed it a little bit to suit more in the acute setting and specifically trying to address the opiate related adverse events. And again, it was part of the multicenter studies where about 300 something patients that we initially tested in one population and validated in another population, looking at inter-variable correlations between the validated group and the initial group.

So it's validated in that sense. And as I showed you the data, there was a correlation

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between the amount of opioid use and the opiate related adverse events. But to your question how meaningful is it to the patient, I think that we asked that question about frequency, severity, and bothersomeness, trying to get to the patient where some adverse events may happen. But if a patient is not too bothered about it, they will score differently from if they are tremendously bothered about it. So that is the extent that it was developed.

DR. SIMON: So I just want to extend that just one second because, fundamentally, we should not be designing any kind of outcome measure, if we think it's important to do that, in the purpose of this particular meeting, unless we actually initially do it, a la, the way the NAP [indiscernible] -- Nat did -- which includes patients from the get-go. And it's critical for us to be able to understand what's meaningful to patients in that regard.

Just as an aside, OMERACT this past year had a meeting in Australia where for the first time, we

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actually asked the patients about safety. We've really never done that before, and most people have not; what's meaningful to them about safety; what are the issues that they care about in the context of rheumatologic design trials. And it was extraordinary what we learned, and I would urge everybody here to think about if you're going to embark on developing such an instrument, that we do it in the context of understanding what patients are interested in. Thanks.

DR. DWORKIN: Bob Dworkin. At lunch, I promised Nat that I'd ask him what I hoped was a tough question.

I take that from a patient -- and this is very relevant to TJ's talk, too. I take the point that from a patient's perspective, constipation, vomiting, nausea, sedation, dizziness are things to be avoided. And certainly as a patient, I would want to avoid those side effects at all costs. But we're not having this meeting, I think, because of those side effects.

We will never have a meeting on gabapentin

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sparing, and gabapentin has bad side effects, too. It causes dizziness, and sedation, and really excessive weight gain. But I'm pretty sure that ACTTION is not going to support a gabapentin-sparing meeting. Lee might like us some day to have an NSAIDs-sparing meeting, but I'm not sure that's gonna happen either.

I think the reason we're having this meeting is not constipation and nausea. I think it's clinically meaningful respiratory depression, overdose, and abuse and addiction. So if you agree -- and I hope you don't actually. There's a part of me that doesn't want you to agree with this. But if you agree that the reason we're really spending two days in this room is about overdose and addiction and what's going on in the country, then it seems to me that we shouldn't really be talking about symptoms and side effects and improving postoperative recovery.

We should talk about preventing patients from getting on opioids. Maybe when they get discharged, they don't get a prescription for

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Vicodin, and maybe that's the endpoint. Or if we can't prevent patients from initiating opioids, the other endpoint might be getting them off opioids. If those are our key end points, preventing initiation and discontinuation, that means the clinical trials that we're going to be designing are very different than a clinical trial showing less constipation.

That's my question. Is it difficult enough, Nat?

MALE VOICE: [Inaudible - off mic].

DR. DWORKIN: Or TJ?

DR. KATZ: It seems like Sharon's willing to take the first shot on that.

DR. DWORKIN: Sharon is fine.

DR. HERTZ: Thank you. I am fine today.

So just as an interesting comment related to what Bob just said was we had an advisory committee. I mentioned it. I took the Exparel slide from there. And we were having all these conversations about the amount of opioids that were used or not used during the clinical study,

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in-house thing. And then committee members said, "Why does any of that matter if they still go home on an opioid?" with the idea being, potentially, you're not going to get away with replacing somebody's knee without some opioids, but really the opioid-sparing benefit would be something other than that interoperative period. But perhaps really preventing the need for opioids as an outpatient, and therefore reducing the amount of opioid available in the community if there's leftover and so on.

DR. KROENKE: We'll finish this. Yes? TJ and then Nat.

DR. GAN: Interesting observation. And imagine yourself, Bob -- god forbid that you don't need surgery. Let's say imagine you needed a surgery. You're now in the post-op period lying in your bed. You are nauseous, 10 out of 10. You are throwing up. You are constipated or you haven't opened your bowels for the last 3 days. You cannot pee, and someone's going to come in with a catheter to put into your bladder. You are delirious.

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You like to be in that state?

(Laughter.)

DR. GAN: No. I understand that you are talking about the major event, respiratory depression, death; I get that. But are we saying that those are actually great states for the patient to be in?

DR. DWORKIN: TJ, I completely agree with you, but that's a different -- I'm going to be provocative. That's a different IMMPACT meeting. That's an IMMPACT meeting where Henra Kellick [ph] would be here. And we have no surgeons in the room. We need surgeons here. We need more anesthesiologists. And that would be a meeting on research designs for clinical trials of multimodal analgesia.

So I completely agree with where you're coming from, but this is a meeting on opioid sparing in the context of an opioid epidemic crisis. And to me, then the key outcomes are death from overdose and substance-use disorder, OUD.

DR. KROENKE: So here's what I'm going to

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do, then I'll let comments come back. I'll take a few from the room. Back there, you stood up, and then you. You must have been excited, in the back of the room.

DR. STEINER: Yep. That's me. Deb Steiner again. Hi.

I guess for me, it would be helpful to -- first of all, when I first looked at the agenda for the meeting, we're talking both about acute and chronic pain, which I found really exciting, but they're very different. And I think the outcome measures are going to be different.

Also, I completely agree that the side effects -- I mean, these are all serious, they're important, but we're talking about pain and we're talking about efficacy. And I hope that we focus on that pain intensity part, too, because as much as the patients don't want nausea, vomiting, and constipation, we're administering these medications because we don't want them to be in pain.

So I just think to me, a little bit, kind of

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stepping back at a higher level and just the broader approach would make it a little easier for me to kind of follow what kind of outcome measures. And certainly the issue with acute that's similar to chronic is the idea of even initiating opioid treatment and where that might lead. Thank you.

DR. KROENKE: And you, yes?

MS. COWAN: A couple of things. I'm sorry. Penny Cowan, American Chronic Pain Association. Sorry about that.

One of the things I want to say is that I've heard, sometimes, patients mention -- and I guess since I'm that voice of the person living with pain -- is that there's a saying, "Nothing about us without us." And I think that starts at the bench in research. So keep that in mind, that there is nothing about us without us.

But then I have to wonder, what is the motivation for pharmaceutical companies, if we're talking about opioid sparing, to say we want to make less of your drug? I mean, I can't see that's a motivation for a lot of them. But then my real

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question is -- and I don't know whether it's to Nat or not -- when we're looking at measuring pain, it's so subjective for everyone. Why are we looking at measuring their level of function, and why aren't we asking them what is their expectation out of this treatment, whatever it might be?

I mean, there are so many components to living with pain other than just taking the medication. But we set everyone's expectation up for I'm going to give you this pill and it's gonna make you better. That's our expectation without knowing that part of that responsibility is ours, but part of it is we need other components. And I don't ever see that in trials. I would love to see a multidisciplinary pain trial done to say this is the way to do it so that payers will begin to pay for it.

DR. KROENKE: What I'll do is I'll alternate, because I know John has his hand up. But I think either Sharon or Nat both had -- and this isn't linear; it might have been on a previous comment. But any comments that you have, and then

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I'll take a couple more from the audience.

DR. HERTZ: I actually disagree a little bit with Bob, and maybe we didn't invite all the right people, but there are two aspects of this. One is when an opioid is necessary because toradol isn't enough? How do you lessen the negative effects? It's a quality of life, quality of experience, kind of issue. I see that as predominantly an acute pain issue, but no, it's also somewhat chronic or true for people with chronic pain.

The second part of that is one that's really curious to me because if we're trying to replace opioids because there's a large amount prescribed and there's a large amount sitting in medicine cabinets and getting into the wrong hands, are we talking about the development of novel non-opioid analgesics, and is that actually opioid sparing? So that's my question.

DR. KATZ: I guess I would agree with Bob that it would be a good idea to determine what this meeting is about relatively early in the agenda.

(Laughter.)

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DR. KATZ: So in that sense, I agree with you, at least agree with the question. When Mao Tse Tung took over in China in 1939, 80 percent of the men in the Pearl River region of China were addicted to opium, and it was a huge societal problem. That's why they had to opium wars, which the emperors were both defeated.

So what did Mao do about his opioid epidemic? He made it capital punishment to import opium. He took all the addicts and put them in sanatoria. Opioids became unavailable in China for 40 years or what have you, even if you're writhing in cancer pain. And the opioid problem was gone.

So if that's the type of opioid sparing that we're talking about, sure. We can have a meeting about that. None of us are probably the right people to be in the room -- and maybe Eric but nobody else --

(Laughter.)

DR. KATZ: -- since he's the only person who really talked about that.

My experience with the IMMPACT group is that

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we're generally talking about how to design and conduct clinical trials that inform scientific and therefore regulatory decision-making in the context of drug development. Even though we take great pains to say that it's not the case, well, it kind of is the case.

So if we're going to say something useful about opioids sparing in that context, it's probably more about the design of strong, non-addictive opioids, and designing therapies that accomplish what TJ said, which is to reduce the burden of opioids. So that's why I came at it from that point of view. But if we're talking about every imaginable intervention to reduce the societal burden of the opioid problem, well, yeah, I agree that that's a rather different kind of meeting.

DR. HERTZ: This is Sharon. I just have to interject so that I don't actually have to leave right now. This meeting does not have anything to do with anything for any regulatory body. This is a discussion of the current state of the science

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and knowledge of a number of highly experienced people in the field. And any attempt to influence regulatory decision-making should be taken out of whoever's thoughts may have them.

(Laughter.)

DR. KATZ: And of course, that's exactly what I meant.

MALE VOICE: I'll add also policy.

DR. KROENKE: Dennis, and then John, and then the other two people.

DR. TURK: This is just to clarify. Sharon, before you got here -- because you came a little bit late -- my introductory comments to the group specified very clearly that this was not designed to address regulatory issues, but rather to inform people of how to do the studies. So I tried to make that point in, and that should be in the record somewhere.

DR. KROENKE: Good. Okay. John?

DR. FARRAR: John Farrar, University of Pennsylvania.

Bob, you talked about the purpose of the

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meeting. And I actually think that a tremendous benefit to the production of interesting studies moving forward would actually be to define the different types of situations in which opioid sparing are thought about and dealt with.

If we think about the relationship between analgesics and addiction, there are different populations. The ones that got us into trouble were the young people who had their molars extracted and got 30 Percocet, and at the end of 30, really liked the way they felt. Hopefully, that's not happening anymore.

In the acute pain situation, clearly we want to limit side effects. TJ was just saying we want to limit potential respiratory depression. We want to do things. we want to use the lowest dose of the harmful medicines that we use; not just opioids but other things as well. So looking at that in terms of how we can spare those side effects or deal with those side effects is an important component of it. Whether I reduced the morphine dose over the 4 days that it's needed by 20 percent

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or 30 percent may not make any difference unless it's dealt with in terms of the side-effect profile that is dealt with there.

Obviously, if we can get an opioid-sparing effect and we send people home without opioid, that's a good thing. You suggested that as a potential outcome; can we get them off sooner or to a lower dose sooner. So those I think provide some parameters to that.

In the chronic pain situation where we have patients who are on chronic opioids already or who might benefit from chronic opioids, and there are such patients, then we want to think about the lowest potential dose possible for those folks. Those are generally not the abusers. Right? They're in general not the people who end up with OUD. They misuse occasionally and so on. And I'm not talking that there aren't any; there clearly are. But it's a different issue, and in that situation, opioid sparing and reduction of opioid might be a very interesting idea.

One idea is let's just substitute every

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third pill as a placebo. There's very good evidence in animals that it works great. So there are ways to get around it. But the goal there is not to get them off the opioid necessarily; it's to make them better on as low a dose as possible.

I guess the question that I have actually is targeted at Sharon, which is you actually said that you needed to take the population into account, the social benefits. And I guess I'm wondering which population we're talking about and whether there's been a discussion about those various populations we just spoke about, because I do think that from a societal perspective, way too many opioids are prescribed, too many in the medicine cabinet, et cetera. But that's not really about opioid sparing; that's about proper prescribing, proper treatment, and so on.

So what group are we trying to think about when we deal with these things?

DR. HERTZ: Just trying to think of where to start this because it's got a few pieces. When we make a regulatory decision, we have a number of

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elements to that decision-making. There's the proximate data that are in front of us, what is it telling us about the clinical trials; the way the drug was studied; the way the effects of the drug, both positive and negative, were demonstrated.

We think about how that particular drug fits into the general availability of other therapies. We think about relative benefit, relative risk in an abstract kind of way because who wants things that are worse without any benefit to offset that worse in whatever way you want to characterize it?

Then we also think about the big picture. When the first transmucosal immediate-release fentanyl for breakthrough cancer pain was under consideration for approval -- for those of you who are trying to remember which one that was, it was a raspberry-flavored, sugar-sweetened lozenge on a stick.

MALE VOICE: Lollipop.

DR. HERTZ: We don't use the L word.

(Laughter.)

DR. HERTZ: It's a lozenge on a stick. And

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the division, which predated me -- just so you know why I'm referring to it as the division -- had great concerns about what was going to happen with this dosage post-approval, and in particular, children.

So that has nothing to do with the patient. It has nothing to do with the indication. It's fentanyl. We already know a lot about it. It was going to go out as a schedule II, but it was a population completely independent for the patient. That's one way we look more broadly.

If somebody came to me and said -- us, not me, us. If someone came to a regulatory body and said we have this new opioid analgesic, it does not cause any constipation and it doesn't cause nausea, but it has the ability to impart tremendous reinforcing properties; although it would have to be scheduled II if it was going to be any schedule, it really looked different than comparators in those type of human-abuse liability studies.

That product has to be considered from a number of perspectives, again, the proximate ones.

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But what is the impact of such an approval? Is there any way of preventing the widespread mayhem that could result from such an entity being on the market? And that's where we really start looking at the public health impact and the population in a broad way, because you can't make any of these decisions in isolation. You have to look at all the different levels that may be involved. And for some products, the public health impact is really not a major factor because little to no impact is expected.

If I have an application for a different formulation of an existing product that has a similar PK profile, that's not quite the same thing as that completely hypothetical situation that I described, which could be quite harmful from a public health perspective.

DR. FARRAR: And where does opioid sparing fit in? I like that description, and it makes it very clear. And I remember Actiq and all of the discussions about that, and there were some real serious concerns, and still are.

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Where does opioid sparing fit into that because it would help -- you raise the question of how much opioid sparing is clinically relevant, and I think to understand what we're targeting and ultimately doing would be helpful in knowing where to go with that.

DR. HERTZ: It depends on what the specific program is targeting. Is the program trying to make the management of pain more tolerable from a global sense for patients? How does that impact the use of opioids in general? Is it really targeting replacing opioids with something that has a different safety profile, perhaps one that's not reinforcing?

So there's no single answer, but I think it's a continuum, Bob, in particular, that reducing postoperative nausea and vomiting is one end of the spectrum. Reducing chronic endocrinopathy for a chronic patient is another piece of that. And lessening the amount of opioids in the medicine chest in the community is perhaps the furthest end.

Then what I see as more of a parallel thing

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is in fact the development of novel non-addictive analgesics, which some people include in the concept of opioid sparing. But I have a harder time seeing that connection. It's still an important one, and its effect may be less need to prescribe other products, including opioids, but maybe it's got such a great safety profile that we don't have to worry about NSAIDs so much anymore.

So there are bigger ripples than just opioids in the novel category.

DR. KROENKE: Now, I' going to take some questions from the group. You had your hand up here.

DR. RATHMELL: Jim Rathmell from Brigham and Women's. Sharon, I think you really nicely clarified what you said earlier -- and this is more for the record so that we don't lose it. You said earlier, if we have these small changes in the way an opioid works that actually reduces analgesia for the patient but results in some small difference in the amount that gets out into society, you probably wouldn't view that very favorably because you're

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going to favor the patient in this one, the individual patient as you look for regulatory. But then if there's something broader that increases the risk to society, obviously it has to be weighed in. And I think that really came together nicely in this discussion.

The other part is about what Bob has said. He's gone all the way to the extreme of opioid related deaths from prescription related opioids. That's probably not an outcome that we can measure in a meaningful way, but what we could look at is where there's a huge signal. And that's persistent opioid use in new users at a certain point in time. So I don't want to just say surgery because I think that's just limiting it. People get opioids for the first time, and they feel God's breath on them, as Eric has said, and they go on to persistent opioid use. And that's a pretty big signal, 6 to 15 percent, depending on where you look.

Maybe that's one of the areas where we can really work it into the clinical trials because if you have 10 percent of something in some

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population, that's very measurable, even in relatively modest sized clinical trials.

DR. HERTZ: Can I just follow that question up?

DR. KROENKE: Yes.

DR. HERTZ: But what does that look like? Does that look reducing the amount of opioid use so that it's not producing those effects or does it mean replacing it with something else?

DR. RATHMELL: It could be any of the above. It could be cognitive behavioral therapy. It could be brief interventions after surgery. It could be nonpharmacological or it could be pharmacological. But the outcome measure could be persistent opioid use 6, 12 months down the road. And if we have 10 percent of a population that never used them before, had never been exposed before, and we can cut that in half with whatever it is, the intervention -- because we're looking broadly, not just at pharmaceuticals, but at other ways that we might approach this problem, and that could be a very meaningful outcome because it's very

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measurable.

DR. KROENKE: So just a comment. I think it's clear that some of the kinds of issues people are bringing up lend themselves to an FDA type of clinical trial, and others are going to lend themselves more to an NIH type of trial in relation to things. So it's non-pharmacologic comparative treatments, if it's complex interventions, I think some will lend itself.

Yes, sir? Back there? Name and where from.

DR. C. BROWN: Yeah. Cole Brown, Innocoll. This discussion in tandem with something that was said earlier has made me think about one perspective of this opioid-sparing challenge that we have. It was mentioned that the FDA is working with sponsors to look at, based on their drug product, the basis for a difference in opioid consumption, what that means.

I think the way the sponsors have looked at the 2014 guidance around the management of acute pain has been looking at the visceral versus non-visceral pain management aspect of postsurgical

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pain, and either correctly or incorrectly interpreting that to evaluate soft tissue and hard tissue pain, postsurgical pain. And within that, looking at their drug products individually, so looking at can they improve pain and reduction in pain in a soft tissue pain model versus in a hard tissue pain model, like a total knee arthroplasty.

I guess my question is to both Tong and Sharon, that as we're thinking about these different opioid-sparing measures, do we think they will need to be specific to the individual procedures or can they be in broader buckets? I'm not trying to complicate things or saying I think one way or the other, but the outcomes related to opioid use might be a little bit different in a patient who just had a total colectomy or bariatric surgery compared to someone who had a breast augmentation or something else superficial like abdominoplasty.

DR. KROENKE: TJ, do you have any comments about that, or anybody? Was it a question you had or did you want those comments for the record?

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Because you spoke to that as well.

DR. C. BROWN: That was just a question on should we think about -- the opioid-sparing measures, should we be thinking about them in a way that should be specific to different surgical procedures or different patient populations.

DR. KROENKE: I guess maybe either one of you, a short answer, and then I'm going to have Eric makes some comments. In other words, is the research design, or questions, or how we do it different based upon procedure.

DR. HERTZ: I don't know. What is the drug supposed to be doing and how does one demonstrate it? And then you can determine if it has something, a limited niche or a broad niche. I don't know. It just kind of depends.

DR. KROENKE: Eric has some comments.

DR. STRAIN: I wanted to jump in. First of all, I'm still a fish out of water 3 or 4 hours later. But I'm enjoying being a fish out of water. It certainly prompts me to think sort of outside of the box.

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Pardon me?

DR. HERTZ: You're an amphibian.

DR. STRAIN: I'm an amphibian. Yeah. I'm crawling out of the water --

(Laughter.)

DR. STRAIN: -- and gasping for air; story of my life.

But it seems to me, as sort of an outsider looking in on this, sparing is a strategy. And I'm perhaps responding to Bob's question from 15 or 20 minutes ago now, because there are sort of two domains of concern that strikes me of relevance, as a strategy, to address either the problems t the individual level or the problems at the societal level. And I'm not necessarily raising anything new. I think I'm just trying to crystallize my thoughts about this.

Sparing at the individual level is trying to address the adverse consequences that the individual is having, as TJ and others have brought up here. And it seems to me that that involves ultimately lowering the dose of opioid that's being

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exposed. So if you can get them on a lower dose, the individual, hopefully you'll have less of those adverse consequences. And then how do you do that is sort of the logical step there. Do you add in a non-opioid analgesic? Do you use a device or whatever in order to address that? And those seem like ideas that could be pursued in.

Let me tangentially mention, this seems like where the HEAL Initiative, wherever those to NINDS guys went off to. This looks like the Clinical Trials Network for pain, to me. This looks like what they should be doing.

The second area of domain, though, is the societal ones, which of course I highlighted in my talk and I find of interest because that's the diversion and misuse and overdose. And sparing that decreases diversion, misuse, and overdose is critical. And there, it's not really lowering the dose; it's lowering the number of doses that are being used that becomes critical. So it seems to me there's sort of a bifurcation in strategies because lowering dose is one set of trials, but

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decreasing the number of doses is another set.
Now, you could also say, well, at the individual level, decreasing the number of doses, if you come up with the holy grail of a non-addictive morphine-like analgesic, which we've only been trying to find since the 1920s, without success, if you can do that, then that accomplishes that as well. But I think in the meantime, we should think about lowering dose at the individual level, lowering the number of exposed doses at the societal level, and then that raises a very different set of potential circumstances as to how do you do that, like prescription drug monitoring programs, CDC guidelines, all of these things which are trying to address that.
So I felt obligated to say something since I've been sitting here for 40 minutes, and now I'll shut up and let you go back to those other deliberations.
DR. KROENKE: [Inaudible - off mic] gasping for air.
DR. STRAIN: Thank you.

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DR. KROENKE: Rich? Name and where.
DR. SCRANTON: This is Rich Scranton from Pacira. I'll give you the context. I'm talking from the context of acute pain and a non-opioid, with the understanding that in this country, and you just stated, we pretty much use opioids as our go-to therapy, particularly in the postsurgical arena or in the acute pain arena. And I really like the idea that we're talking about composites, as something coming from my cardiovascular epi background, on an outcome. But then we also heard about tearing it apart. We're talking about analgesics, so we've got to talk about pain intensity, but they are all related from the patient's perspective.
I've been attempting to try to tease these apart and then put them back together because patients are going to make choices on their pain, and their opioid related side effects, and function, and the choice of therapy also may impact. A patient who just had surgery who can get up and shower because they're not in that much pain

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and not sedated because of opioids actually has a positive feedback on the psychology, so an integrated scale that actually combines the pain, the side effects, in this case, compared to opioids with function.
Then perhaps agreeing on surrogate endpoints that predict a behavior beyond that initial, some of the registry work that we're doing, I think that's what I feel like I need, because I'm also perplexed that I can diminish severe pain after surgery, and yet patients are going out with opioids far in excess than what they were taking during the acute incident when that was the most severe pain. And that's something I'm grappling with, how do I change that.
So a composite that integrates these in surrogates that we can agree that if we could impact those, those would have the outcome, the most desired outcome.
DR. KROENKE: We have a little less than 15 minutes left, so I'll continue to take questions. And I think at some point we'll recognize that

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what's good is some of these will be comments for the record that we'll be able to incorporate in our report, and others, we'll have selective commentary from the panel. So I'm going to be looking to the panel to put your hand up if you have a real strong comment; otherwise, I want to get as many comments out there as possible.
Yes, in front? Michael? Name and where.
DR. ROWBOTHAM: Mike Rowbotham, Sutter Health and UCSF. I have a question. Let's say that somebody came up with an opioid that had all of its reinforcing qualities, all of its analgesic qualities, and maybe a little less tendency to respiratory depression. But it had dramatically less endocrinopathy, itching, nausea, vomiting, constipation than everything else. So you'd have all the societal harm because one would presume this would be super addicting. Right? Because it has so much less downside.
So the reason I bring up this is are we looking to reduce the adverse events of opioids but not so much that we create a super opioid?

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DR. KROENKE: I'm not going to require anybody, but that's a good -- does anybody want to comment on that?

DR. HERTZ: I think there are a couple ways one would have to look at the data for that kind of a product. There are reinforcing effects that are positive usually, and then there are the negative effects that can take away. We'd have to try and sort through that and look at the balance. I don't know what the actual answer is for something like that, but it's a very challenging problem. And I'll tell you where it's come up in a more proximate way.

We had a product that went to advisory committee, so I can talk about it. It was a hydrocodone-acetaminophen combination with promethazine. And the idea was it would reduce nausea and vomiting. And trying to get a signal detection, the population was somewhat enriched for people who are likely to have that.

one of the questions that arose was, if we take away the nausea, will people be more inclined

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to abuse this, and is it going to be more of a gateway drug? And we tried to look at it a couple of different ways, for a different reason because for promethazine has CNS effects. We worry about additive effects. When we told people to use less opioids, they started using gabapentinoid. So lo and behold, now everyone's worried about gabapentinoid. So we're trying to avoid some of these surprising, or perhaps not so surprising, events.

That product was studied in a human-abuse liability study, and I'm actually not completely familiar with all of the details. It's been replaced by a lot of other products subsequently. But that comes up all the time; when you're looking at reducing symptoms, negative symptoms, what else happens?

Some of the scales that are used, we look at these human-abuse liability studies, and we rely on them for a certain type of information. For those of you who aren't familiar, you take traditionally a non-dependent but experienced, what we call

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recreational opioid abuser, and you give them a couple of different things, and you have them rate it on a number of different skills. There's some qualification phase; it's not important right now. And they are asked to rate positive and negative effects.

One of the scales that I particularly like is the use of a bipolar scale that has neutral in the middle, like it a whole lot at the top, and dislike it a whole lot at the bottom, which is a way to try and integrate some of these different things because we know that in certain circumstances, a product that can get you very high, which is one of the scales, you may not like, maybe because we put something irritating in it so that it would be nasty when you snorted it or what have you.

So I think that kind of an assessment is really important when we start getting into perhaps opioids that have some of these properties.

DR. KROENKE: Eric has a comment.

DR. STRAIN: I like your question a lot,

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Mike. It strikes me that we kind of have that experience, which was barbituates and then benzodiazepines, and look where that got us. Right? So I'm not sure I want to pursue your product.

(Laughter.)

DR. KROENKE: Nat, comment, and then questions.

DR. KATZ: I like the question a lot, too. It's very thought provoking. It also reminds me of the concerns people had about the HIV drugs when they came out because, oh, we're going to give people these HIV drugs, but then they're going to go be more sexually promiscuous, and that's morally evil, and we don't like that. So there was this very kind of theoretical anticipation of how many rungs outside of the patient, people's behavior, would be changed in some undesirable way.

I think making treatments that work better for patients is a good thing. It's a societal good. It's a blessing when we can do that. And I don't think that these theoretical concerns should

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stop us, in particular, because -- and I'll ask Eric for his support on this --

DR. STRAIN: I'm always behind you.

DR. KATZ: -- thank you.

We, for example, did a study of adolescent prescription opioid abusers a number of years ago and published it. And they were into snorting buprenorphine, and what they said was that they would snort buprenorphine, and they would look, hopefully, waiting for the moment where they would start vomiting because they knew after they started vomiting that they would start to feel high again. And you see all these examples where the side effects don't seem to bother people with drug addictions.

So if you were to make one that was less nauseating or whatever, I think it would be a mistake to assume that that's automatically going to be like some kind of scourge on the planet of a new more abusable drug. So I say let's help the patients first.

DR. GAN: Just another comment on your

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question and also Sharon's response, I think, to an extent, get to what Bob's earlier question is. There's a whole range of opioid adverse events. You've the annoying , unpleasant nausea, confusion, all the way to respiratory depression, and death. And I think that the drug, as Sharon mentioned, if it had been a drug that would reduce instead of nausea with a combination product, that it would reduce respiratory depression and death, I think the panel's response would be somewhat different.

I think it also gets to that gradation of severity, know, how bad are the side effects and whether it causes death or not. And to that question, I think that it's a conundrum because know from the company perspective, they are trying to develop drugs that reduce maybe one of the opiate side effects, but at the same time, then, would it be open to more abuse? Now that they have no nausea, therefore they can use more of it. So it's an interesting question.

DR. KROENKE: Why don't I do this? I'm

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going to do the last 5 minutes. I'm going to just allow people to get their comments or questions out [inaudible - off mic] by the panel, just because I'd like to maximize the number of issues that go on the record.

So starting in the back, somebody had their hand up. So make your comments relatively brief for the record. Yes? Back there? Someone had their hands up. You had your hands up. Yes, right there.

DR. SCHOLZ: Joachim Scholz, working at Biogen. Mike's comment is actually not so off reality. When I was still at Columbia University, we were working actually on a bias opioid receptor agonist that spares the Arestin via the [indiscernible] pathway; less side effects of the kind we have talked about, but the addiction liability is still unknown. It's a good analgesic. There are several of them in development.

I think the main reason we have this workshop is really for limiting the addiction problems. So I think if we develop alternative

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opioids that spare some of these unwanted effects that patients feel immediately, it still doesn't solve the problem. And I would not considered that opioid-sparing strategy. I would just say it's a different opioid that we develop, but it doesn't solve the societal problem, and I think that needs to be considered when we talk about research design for opioid-sparing strategies. So they have to be long term that capture these other problems and not just focus on nausea, vomiting, or respiratory depression.

DR. KROENKE: Yes?

DR. MADSEN: I'm Torsten Madsen with Aptinyx. I just want to comment that I don't think the comment that Penny Cowan made on the patient perspective was addressed. Secondly, another comment that we have an awfully granular view of the side effects of opiates, and yet we accept that the view of pain in general is best measured with a scale that goes from zero to 10 and our view of that. So do we want to retain the same pain level in an opiate-sparing trial? Are we okay with just

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sticking to the NRS?
I suggest that there's some thought put into maybe becoming a bit more granular on the characterization of the pain that we're trying to either maintain or alleviate, along with this incredibly detailed view of vomiting and nausea, and all that, which is not unimportant either. I get that.
DR. KROENKE: Yes. So I'm hearing you're saying we need to balance the depth and granularity to measure the pain as well as the side effects.
DR. MADSEN: Yeah, and think about maybe if there is a tool that could be better in describing what it is we're trying to achieve with an opiate-sparing drug as it comes to remaining.
DR. KROENKE: I see in the back, and then you.
DR. WENTWORTH: This is I guess a question/comment --
DR. KROENKE: Name?
DR. WENTWORTH: Sorry. Kerry Wentworth, Flexion Therapeutics. Sorry. How many times have

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you heard that today?
A question or a comment to Nat. I really appreciate your presentation, and perhaps when you go back and look at the definition you propose for opioid sparing, adding a word "avoidance" in could also be considered because I think that that may get to the point that Eric was trying to make, that you can spare dose and you can spare number of doses, and I think sparing that number of doses to the point of avoidance would be really important.
I can't help but jump into the weeds in some of the clinical trial design considerations that you've put forward. For full transparency, we worked with Nat a number of years ago in trying to design an opioid-sparing trial in the chronic pain setting. We got super cold feet. Although it was the cleanest design providing opioid as a rescue medication for a company that's dealing with a non-opioid, it was something that we just didn't want to get in the business of.
So that's sitting on our shelf right now, but we really have continued to think about how do

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we do something in the chronic pain space that's not full of noise and we can get a signal on. So appreciate others' thought about giving an opioid as a rescue medication, as to whether that's viable, would be helpful. Thank you.
DR. KROENKE: Last comment here, and then we'll move on to the afternoon session. Yes?
DR. HAYTHORNTHWAITE: This is Jennifer Haythornthwaite at Johns Hopkins. I'm struck by the point about granularity and the issue that we're talking about, a number of different really important concepts that we have talked about in the pain field for decades. So we're talking about pain assessment. We're talking about side effects, which we probably haven't had as much discussion in the pain field as we should, and we're certainly not organized in our measurement the way we are in other areas.
We're also talking about function. So again, a lot of the work that the IMMPACT group has done, we haven't talked about negative affect. We haven't talked about some of the other kind of

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factors that drive people's taking of medication. We haven't actually talked about the measurement of medication. When people are in the hospital, you have much better access to what they take, when they take it, and how much they take it, et cetera. Good luck doing that out in the field. We've tried. It's really hard.
So the purpose of this conference I think is to potentially introduce a new concept, opioid sparing. It's one that's come from the press. It's come from the recent deaths. It's come for a variety of reasons. But I think the challenge I'm having sitting here is to what extent we think of opioid sparing as a new concept versus a merging of existing concepts that we already have and have thought about. So I think that's something that we're going to have to continue having the conversation.
I've heard a couple of different operationalizations that are different than we typically use. And the one that I have liked for a long time from the drug abuse literature is the

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likeability scale that Sharon mentioned because it really is a very -- it's kind of the marker of whether an abuse has substance abuse risk. And we have not yet done that in our field much at all, that I know of. It's probably woven into some of the laboratory studies, but it's not at all woven into the clinical patient groups.

Obviously, patients would need to weigh in on that in the process, but that combined with some of the operationalizations of how do we measure opioids and do we see reductions in their use, I think in my mind are getting closest to the concept of what I thought we were going to be talking about when we talked about opioid sparing.

DR. KROENKE: I'm going to have to, unfortunately, bring it to a close, a lot of good points. There's more discussion today and tomorrow, and particularly tomorrow afternoon. So I'm going to turn it back to starting the afternoon session. I want to thank the panelists.

(Applause.)

DR. DWORKIN: I'm Bob Dworkin, and we're

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going to segue right into the afternoon session, and that's going to be chaired and moderated by Professor Jim Rathmell. He's professor of anesthesiology at Harvard and chairman of anesthesia at Brigham and Women's Hospital in Boston.

Thanks very much, Jim.

DR. RATHMELL: All right. I'm your tour guide for the afternoon, and on we go. We have a number of a fantastic presentations this afternoon that I think are really going to expand on this and hopefully bring new perspectives. The first is Shannon Smith. Shannon's at the University of Rochester in the Department of Anesthesiology, where she's assistant professor. And she's going to talk to us about scoping the review of methodologic characteristics of both acute and chronic pain clinical trials of opioid sparing. So I guess you're going to tell us what's out there.

Thank you, Shannon.

Presentation- Shannon Smith

DR. SMITH: All right. So I'm going to

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change the focus a little bit to more about what's happening in the literature than to try and answer some of these huge questions that we've identified here so far.

The first thing I just want to say is that my name is slapped on here, but there are a lot of people that I want to thank for their help in this. In particular, Bob Dworkin; Nat Katz; and John Markman for helping to develop the coding manual, and a real special appreciation to Jen Gewandter for helping with the coding manual and for helping to do the coding, which is a big plus in my book.

I also want to highlight that this is about the methodologic characteristics, so nothing about the efficacy of any of these opioid-sparing techniques and interventions. I also wanted to point out here, too, with the trials of opioid sparing, as you'll see, it's not always the primary purpose in these studies, but we tried to identify articles in which opioid sparing was a focus in some way or another.

A scoping review is actually sort of new to

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me. Many of you are probably familiar with it. But basically it's trying to get a lay of the land and to kind of see what's out there without finding every single clinical trial that is doing something related to opioid sparing. So we included trials that were randomized controlled trials and treatment of acute or chronic pain patients, so not necessarily to reduce their pain, but just that those were patients who were enrolled. So people who had chronic pain and they were trying to reduce their opioid misuse, and looking at opioid sparing as an outcome, those kinds of trials would be included here. Adults 18 and older and opioid related to outcomes, so things like the opioid dosage, opioid sparing, and opioid related adverse events or side effects were included.

We did a PubMed search for certain texts words, and we came up with 255 articles. So it's clear that we were very narrow in our search. We used text words like "opioid sparing," "narcotic sparing," "morphine, sparing," and other things like those words, and that led to 255 articles.

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You probably can't see all of this, but basically we excluded a lot of things because they didn't meet our criteria. They weren't clinical trials. They included children. But I want to highlight here that we were excluding people or excluding the clinical trials that were acute trials before 2010.

We got a large number of acute pain trials. So to kind of narrow our focus for the acute pain trials, we focused on ones that were from 2010 and closer to the present, up to the present, and that still gave us 73. For chronic pain, we didn't have this limit because there were only 5 that were relevant, so we didn't have that same limit.

Also, the steering committee provided some feedback about potential articles that could be relevant for acute pain and chronic pain, and in reviewing those, we found an additional 10 for acute pain and 17 for chronic pain. So we had a total of 83 acute pain trials, mostly postoperative. One was a postoperative study that went up to a year in its follow up. So you could

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start to argue that it's really chronic pain at that point; one severe acute pain in the emergency department study. The chronic pain trials, there were 22 articles that resulted in 22 studies, so there were some that were reporting multiple studies.

So I'm going to start by talking to you about the acute pain trials, and again remembering that we're focusing on the methodological characteristics here; so what was done in a study; how did they do it; and how were they capturing opioid sparing in these studies?

I wanted to start with the opioid related study objectives. For about half of these acute pain trials, the primary outcome was opioid sparing. For the other roughly half, opioid sparing was a secondary outcome. We thought opioid adverse events was the primary outcome in 2 percent of the trials, and I think in some ways this goes back to the point Nat was making about do we have this gestalt of all of these various AEs, in which case it might be really difficult to show any sort

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of movement because one person has nausea, the other person has vomiting and nausea and respiratory depression; how do you actually have any sort of assay sensitivity to look at differences in that way? These to actually focused on one particular adverse event, so they were somewhat unique. The rest of these, about two-thirds of them, were using opioid adverse events as a secondary outcome. It wasn't really the primary purpose.

Again, this is probably hard to see all the details here, but the interventions and controls that were used in these studies, we lumped into this one first category, anesthetic protocol. Most of these were postoperative studies, so it was things like are they getting an epidural, regional anesthesia, blocks; those things were in that category.

Then there were a lot of pharmacologic intervention, so NSAIDs -- I can never say this, so I call it dex; I think that's what other people call it, too -- antiepileptics, acetaminophen,

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some device behavioral, and then other that didn't really fall into anything else. There was one other trial that was nicotine that was given to patients.

Controls. So over half of them were placebo-controlled trials; 17 percent were trials where it was the active intervention compared to some other intervention that either they thought was already being effective, was already shown to be used well in these patients. And that's a little bit different than this usual care medical management. There, the protocol or the studies were basically saying we compare this to usual care or medical management, which they either defined or did not, and then a variety of other kinds of controls.

Who was included in these studies? Who were researchers enrolling here? As you could probably suspect, the biggest inclusion criteria was that the patient was having a specific kind of intervention, that they were having some sort of surgery, abdominal surgery, knee surgery, that sort

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of thing; and then a variety of other things like how are they going to be in the hospital, what kind of pain are they having. The ED study requires that the acute pain be less than 7 days.

These two I think are interesting because as I was talking with Bob about the results of this scoping review, it dawned on both of us really that Nat Katz always makes the point that when we're doing these studies and wanting to look at things like opioid sparing, we often don't include the people for whom opioid sparing might be an outcome of interest.

Here, these are acute pain studies. These are people who are coming in for surgery. They're at least trying in these two studies to recruit people who are on opioids in some way. So that's great but also contrasted into the exclusion criteria that these acute pain trials were using. So they were excluding people if they had opioids or other substance misuse or abuse; opioid dependence or withdrawal symptoms; chronic pain conditions or selected chronic analgesics; using

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opioid analgesics.

So they're excluding the people for whom we would want to know are these treatments actually going to benefit them. That's sort of a problem if we're going to be able to understand if these treatments work in the broader population.

What were the primary outcomes? How are they getting at what they care about? Opioid dosage as a continuous variable was the primary outcome in 39 percent of the trials, and then some of variations on that. Opioid dosage and pain were the two primary outcomes.

This one is opioid reduction, so they just dichotomized. They came up with some number that they wanted to decide was the appropriate amount of reduction, and either people met that or they didn't. Then they also a couple of studies looked at opioid adverse events, so either self-report measures or observed by the study staff, or pain outcomes were a major -- 13 percent of the studies, so maybe minor would be more accurate, in these acute pain trials.

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For secondary or exploratory outcomes, opioid dosage, again, was frequently used in about half of the trials. Time to first opioid dose was also an outcome of interest in these studies, and then opioid reduction in a dichotomized way. Then one study did an ordinal, like did people take zero, 5, 10, or more than 15 milligrams? And this one, did they go home with an opioid dosage when they were being discharged from the hospital?

For opioid adverse events, most of the studies that were capturing opioid adverse events weren't reporting how they did that. And again, methodologically, that's problematic because we can't compare from one study to another. We can't say, hey, this drug is having these effects on people and it's being assessed in this way, and compare that to another study.

Of those that did report what was happening, it was either observed. People were being asked did you have this symptom, did you have this symptom, did you have this symptom, and the patient just answered yes or no. In 7 of the studies, they

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were looking at charts to see were antiemetics prescribed, were laxatives prescribed, and using that as a signal that the person was having opioid related adverse events; self-report measures also, and then passive capture, just having patients describe what sort of side effects they were having. Then again, pain was being assessed in a lot of the studies as well, or a proxy for pain, and then time to discharge from the PACU was a secondary outcome in two of the studies.

In terms of this how are we assessing opioid dosage, how is it being captured, I actually was thinking the same thing as Jennifer Haythornthwaite was just saying. Acute pain trials have this huge benefit that they have people in the hospital. So there are very few not reported's that were in these trials. They were able to tell how the opioid dosage was captured. So 43 percent was the PCA; 41 percent, it was either being administered by the study staff are they're recording what the patients were taking. They had a real controlled way to assess that; and other variations, so

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combinations of different things were used as well.
How were the opioid adverse events measured? Two studies used a nausea NRS. One was a zero to 10 and one was zero to 5; the Bristol Stool scale; the opioid related symptom distress scale that I think Dr. Gan talked about before; opioid side effects scale; and then this confusion assessment method for measuring delirium in one study.
Before I tell you about the clinical relevance as discussed by these studies -- I'm not going to make any conclusions about the clinical relevance. I'm going to punt like Sharon Hertz did on that question. I'll tell you what they said about whether or not their results were clinically relevant, but I think it's important for us to kind of take a step back for a minute and think about what kind of clinical relevance we really care about.
Do we care about what's happening within patients? So my opioid dose goes down by a certain number of milligrams and I'm feeling a lot better, and that's meaningful for me. Do we care about

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between group clinical meaningful difference? These things are probably both important. The first is likely easier in the grand scheme of things to measure than the second, but I also think, relevant to what Eric Strain was saying, do we also want to be thinking about what's societally clinically relevant.
So I think all of these things are important to keep in mind when we're thinking about these studies. That being said, most of these studies were not thinking about that. Three-quarters of them weren't even talking about the clinical relevance of the results at all. They simply reported this is what we found, and that was it. They said nothing more about the clinical -- I mean, obviously they expounded, as we all do in our articles, about the meaningfulness of their results, but not calling it clinically meaningful and clinically important.
For those that did discuss the clinical relevance, 9 of those studies were talking about the clinical relevance in terms of their sample

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size calculations and saying that they used some clinically meaningful difference; 6 of them provided no reference; 3 did provide a reference, and I'll tell you about those in just a second; 13 trials talked about the clinical relevance in terms of their specific results, saying that their results were clinically meaningful and then providing no reference to back that up; saying that they were meaningful in providing a reference. And then 3 articles, they said either maybe not or these results clearly are not clinically meaningful, but also they didn't provide references either.
There's really no way to judge clinical relevance until we think about what is it that we as a society, as a group of researchers, want to see is the clinical relevance of these results. So let's look at the specific references because I think they can be informative, and I think maybe John will talk more about this clinical meaningfulness when he gives his presentation as well, John Markman.

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This first article referenced a review that showed that Cox-2 inhibitors reduced postoperative morphine use by 10.9 milligrams, and therefore the reduction that they saw in their study was clinically meaningful. No comment on the difference between groups, but comment on within patient difference and in reference to a review of Cox-2 inhibitors. So again, we can take from that whether or not that's relevant.
This article talked about -- they referenced an article that had the median effective analgesic dose of an antiepileptic, and the median effective dosage of that antiepileptic decreased morphine by greater than 30 percent. So they basically used that to claim that a reduction in morphine use of 30 percent or more was clinically meaningful.
This article cited their own prior research showing that 10 percent reduction in -- I can't remember what the drug was now, was clinically meaningful. But they did in this case acknowledge that it was a clinical judgment, so, again, take from that what you will.

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This one I find very interesting. This article indicated that a reduction in the PCA usage of greater than 30 percent is clinically meaningful, and then went on to cite references that it's clinically meaningful because pain reductions of 30 percent or more are clinically meaningful. I guess it's a leap to make that conclusion --

(Laughter.)

DR. SMITH: -- at the very least.

MALE VOICE: [Inaudible - off mic].

(Laughter.)

DR. SMITH: Strangely, it wasn't even citing John Farrar's paper, actually. We can't count it at all.

Then in this final one, they had a reference to explain why they said that a 30 percent decrease in oxycodone was clinically significant. But then when I looked at the reference, there was no talk about oxycodone. There was no talk about clinical meaningfulness, so sort of useless and irrelevant.

That's the lay of the land, as I have been

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saying, for acute pain. I want to focus now on the chronic pain trials because there are a few minor differences as you'll see. Again, for the study objectives, opioid sparing was the primary purpose in about a third of the trials and the secondary in about 42 percent of the trials. Opioid adverse events were always a secondary if they were included, and it was in about a third of the trials as well. And then 19 percent included opioid misuse, abuse, or withdrawal as a secondary or exploratory outcome.

Again, there's a lot going on here, but in terms of interventions, a lot of pharmacologic, but then a few other behavioral things pop in there; behavioral, this multidisciplinary care. So they're seeing MDs and behavioral health, and maybe other kinds of treatment as well. Then for the controls, here we see a lot fewer placebo controls, but we do see a lot more comparison to other opioids. So people are kind of staying on the opioid that they're on, and then they're randomizing the other people to something else; and

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then usual care or medical management, different dosages of the same intervention, and some other controls as well.

Who's being included in these studies? Here, it actually was much easier to lump these into opioid related and pain related. Here, they were including people who are on opioids. These are people that they want to spare the opioids because they're probably already taking opioids, so minimum length of time that they're using the opioids around the clock; something about their dosing; that they are having dependence or withdrawal symptoms; and then also pain related inclusion criteria, that they have some minimum pain intensity or maximum, that their pain is poorly controlled. About half of them also had to have a specific pain condition to be in the study, although that wasn't true of all. Some were just chronic pain in general.

For exclusion criteria, here half of the trials were excluding people if they had psychological or psychiatric disorders, again,

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raising that question about is this opioid-sparing literature reaching the people for whom we might want to be offering opioid sparing? And again, here with about a third of the trials excluding people if they had opioids or other substance misuse or abuse.

This one is a little bit weird. Here they couldn't be using any other analgesics other than what was in the study, so they had to convert to the opioid that was in the study in order to be included.

So what were the primary outcomes in these studies? Here, opioid dosage was the primary outcome in a about a quarter of the studies, opioid dosage and opioid AEs. One study included both of those is primary outcomes; some opioid misuse and abuse or withdrawal studies, and then pain in about a third of the studies was the primary outcome, and then some other things too. There was one study that seemed to be essentially a pilot, and it was looking at whether or not people would stay in a treatment protocol where they had to come off their

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opioid altogether or switch to buprenorphine, I think was that study.

Secondary outcomes, so opioid dosages being captured as a continuous variable in about a third; a dichotomized opioid reduction in 15 percent. Time interval between opioid doses, so are people able to go a longer length of time between their opioid doses? Then again, we're not seeing real excellent reporting of the opioid AEs in these trials either. Some self-report questionnaires were being used; observations in one study; passive capture where people just wrote down what they were feeling in one study. Opioid withdrawal and misuse and abuse, and I'll show you the measures used for that in a minute. Pain was a secondary or exploratory outcome in 81 percent of the trials.

This one I wanted to point out on its own. Russell Portnoy had a study where, as a secondary outcome, he was doing a composite of pain and opioid dose, where it kind of mimics some of the things that we've been talking about here today. So if your pain stayed constant but your opioid

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dose decreased, then that was considered a win. If your opioid dose stayed constant but your pain was decreasing, then again, that was considered a win. He was trying to bring these things together because I agree with Nat's point that we also need to be thinking about what's happening with the pain management.

How was opioid dosage captured? Unlike the acute pain trials where they had people captive, here, self-reports were the most frequently used method. Twenty percent of the trials didn't report what was being done. There was one severe cancer chronic pain trial that used patient-controlled analgesia; that completion of the opioid discontinuation or opioid replacement treatment; a number who were taking their opioid rescue during study visits.

It was really not very clearly written, but it seemed like they were only capturing it when they came in for study visits, so I'm not really sure about that; that they got an IV dose during a procedure or there was one study done where they

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were looking at earning oxycodone doses versus earning money and use that as a way to kind of capture. So it was being captured clearly by the study staff.

How were the opioid related adverse events measured? Opioid withdrawal symptoms were collected in 4 of the trials. The Clinical Opiate Withdrawal Scale was used in two of the studies, the Subjective Opiate Withdrawal scales in one; some self-reports and observations of physiological symptoms in another. Misuse and abuse was measured by the current opioid misuse measure, the Prescription Opioid Misuse Index.

Then actually, I think this might have been one of your trials, Dr. Jamison, drug misuse index that uses a triangulation method. They collect urine, they use the COMM and they use the PDUQ to see if people qualify as misusing their medications; and then constipation as an NRS in 3 of the trials.

So here, there was not much discussion, again, of the clinical relevance of the results.

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Again, about three-quarters of the studies didn't discuss it at all. And those that did, none of them provided any references. None of them talked about it in terms of their sample size calculations. It was always in reference to the results. Four of the studies said that their results were meaningful, no reference; two studies said that their results might be meaningful, no references; and one said they were not meaningful, again, no references.

To sum up all of this, I think it's important for us to know this landscape, to understand the lay of the land, as I've been saying, so that we can understand what's being done; how are we assessing adverse events; how are we assessing opioid sparing, so that we can then make better recommendations as a consensus group to move forward and think about what should be done or maybe what more research we need to be doing. That's the first point.

I think the other key point we need to be thinking about, is it good to be excluding patients

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who might most be in need of the opioid sparing or an opioid adverse event reduction? If we decide that that's not ideal, then how can we include them in a way that doesn't put them at risk? We also have to be thinking about that.

What's clinically meaningful, both within patient and between groups, and potentially societally? I also agreed -- I think this is a really important point -- that we need to capture opioid sparing and/or reduction of opioid adverse events, and pain because although I am thoughtful about Dr. Gan's presentation, where I'm willing to take a little bit more pain if my opioid adverse events reduce a whole lot, but I do think that we at least need to consider these things not in silos. Like they all kind of are related together, and it's important for us to consider them together. Thank you, guys.

(Applause.)

DR. RATHMELL: Brett, while you make your way up here, let's take a question or two, comments. Michael?

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DR. ROWBOTHAM: Were any of the chronic pain studies, either exclusively or include an arm where patients just withdrew from opioids completely rather than a substitution strategy like converting them to buprenorphine?

DR. SMITH: Maybe one of them. Other than that, it looks like they were all being converted, at least in the ones that were included in the scoping review.

John, do you have a point relevant to that? Oh, okay. So yeah, not that I remember, at least in what we found in our scoping review.

DR. MARKMAN: John Markman. [Inaudible - off mic].

DR. SMITH: I'm trying to think back. We didn't specifically code for that, so I don't -- it doesn't ring a bell because Jen and I weren't looking for that when we were coding the articles. It's possible that it was there, and we just weren't looking forward, so I'm not remembering it.

DR. RATHMELL: Thank you very much.

DR. SMITH: Thank you.

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DR. RATHMELL: Next is Brett Stacey, who's professor of anesthesiology and pain medicine at University of Washington and the medical director of the Center for Pain Relief at the University of Washington. He's going to talk about assessing opioid use and opioid outcomes.

Presentation - Brett Stacey

DR. STACEY: Good afternoon, everyone. Thank you for inviting me, Bob and Dennis. And even though Bob said we weren't going to talk about grammar and things and punctuation, and as the hyphen variably appears. So I put mine in parentheses. If you liked the hyphen, feel free to think it's there.

(Laughter.)

DR. STACEY: That's the first thing.

The second thing, I thought I'd start with a little vignette that kind of motivates me a little bit in this area, which is I know a person who was not prescribed chronic opioids, did have a psychiatric crisis, was able to gather up dozens of opioids from prescriptions that had been given to

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various members of the household, and instituted an overdose plan to end their life, and thankfully revealed the plan to someone who then intervened, and didn't happen. But dozens of opioids were found in the household. All have been prescribed for an acute pain condition and then barely used and hoarded.

So we need to think about this. It's not just the chronic pain patients we might be impacting.

If you're an anesthesiologist of a certain age, you may remember this study. I remember it really well because I was very young and impressionable when I read this, and it really influenced me a lot, because at that time I was thinking of myself as an anesthesiologist, which I no longer do. But at the time I did, and I thought this is an amazing study because it shows that your anesthesia technique can influence the pain experience for a long time thereafter. with a short little intervention.

What this was, was an anesthesia technique

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study looking at a double-blind, randomized trial, general plus local infiltration versus spinal. And the main focus of the paper was pain at rest, pain with pressure, and pain with movement up to 10 days after a hernia repair. And here's this data, and this is why I got really excited about this.

Ten days later, you can tolerate more pressure at the site, and you have less pain with more pressure, which means things like putting your seatbelt on would be less painful. So this has real-world implications. It wasn't until a few years later when I went back and looked at this paper again, that I discovered this outcome in there, which is as a marker for the duration of analgesia, they looked at the first opioid dose and showed a huge difference with the local anesthetic group versus general anesthetic; so a big delay in use of opioids.

But like many, many, many acute pain studies, here's one outcome endpoint that shows a reduction in opioid dosing, initially, but did they go home with fewer opioids? Did they catch up the

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net right after they got the first dose? None of that stuff is reported, so it's just kind of out there as a single outcome point, and that's like a lot of the studies that we're going to look at.

Some things are really obvious, but they get stated anyway, and here's an example of that. My first visit to the Seattle Zoo with my son, loved this, and he said, "Whoever would want to pet a porcupine?"

(Laughter.)

DR. STACEY: Which, I don't know, but here we are.

So I'm going to say some things that are obvious, and one of these is a little bit controversial. Opioid reductions are often not the focus of the study, and the data can be buried like in that first study I showed. In general, I think most patients, except for the trade-off of side effects, would say opioid reduction is meaningless if pain is worse, unless you have some other benefit that would overcome that.

For acute pain, there's really no standard

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of how to assess opioid use, the dose reduction, or opioid specific outcomes, but there are a lot of studies that report opioid sparing. And for chronic pain, there's even less consistent data, as we heard the last half hour. And even though there's not tons of data, there is a lot of discussion about it. This is a hot topic.

This is an old paper, but you might recognize an author or two there, saying, "Who cares about the number of milligrams?" And then here's a more recent one saying, "Should hospitals market their opioid-sparing analgesia to patients?" Of course this is in the anesthesia literature. And then this is a good one to think about; "Opioid omission is not opioid sparing." Just because you don't give someone a dose of medication doesn't mean you spared them something. It means you may have forgotten something.

(Laughter.)

DR. STACEY: And this one says, "Oh yeah. We should go ahead and market this." So there's lots of back and forth here, and it's not settled

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out there in the world whatsoever.

I am not going to talk about the pain outcomes thinking there's been 20 IMMPACT meetings about that, or something; maybe 19 of them. So instead, I'm going to talk about how do they assess the opioid use in these clinical trials and what should we think about as standards going forward? So I'm just going to review some of the stuff, and then we can have discussion later about which ones we think are important or not important.

A very commonly important one is time to first dose or the use of a rescue medication. Then there's the dose prescribed, how many pills were prescribed per event or time period; number of pills or doses taken. Then there's something looking at the accounting for the total dosing, MME or MED, or accumulative daily dose.

We will talk about those first three in more detail. Then there's duration of opioid therapy, opioid refills, does the dose go up? And then there's the special case of a dose of zero, a dose of zero meaning you're tapered off or you

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completely avoided the ultimate holy grail of opioid reduction. And like I said, I'm not going to talk about the pain outcomes because I think that's a different topic. This all assumes that there is really not significant worsening or improvement in pain function, side effects, and satisfaction. And there's multiple ways of assessing those and complete inconsistency in the literature.

Time to first dose and use of rescue is commonly used in acute pain studies. I think most of them say that somewhere or another, and assesses the intervention's initial effect or duration effect. If you have a less intense stimulus or a super effective intervention, you may be able to completely avoid the use of opioids.

No one has a clue, as was just pointed out in the last half hour, what is clinically significant here and if it's meaningful as a stand-alone outcome. If the only thing you report is opioid sparing as delayed the first dose, does that mean anything? I don't know, especially if

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you collect the other data but choose not to report it. It might not be.

How does it translate to clinical practice? I really don't know. And does it lead to decreased overall opioid dosing? I can tell you from looking through several of these papers, they showed an opioid-sparing effect in the hospital. All patients in every group got the same prescription when they left the hospital. So it didn't matter if you demonstrated decreased opioid requirements, you still got a nice big bottle to go home with. It's your going away gift. Thank you for coming to our hospital.

The next outcome is MME or MED. Depending on your state, local jurisdiction, and local practices, you may call it MME. You may call it MED. In our state it's MED, morphine equivalent dose. It's pretty clear that the risk for bad harms with opioids are dose related, and the way we look at the dose is to think about the MME or MED. It's reported in both acute and chronic pain studies. In acute pain studies, it's often

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reported only for the first day or two, and then it kind of stops, and it's not thought of anymore.

It definitely has clinical utility, as patients above a certain dose will start having increased risks for events and more likely of having serious adverse events. It's definitely prominent in public policy and guidelines. I know that in my state, in the guidelines for opioid prescribing, that you have to go through the educational course to get your license renewed.

There's MED mentioned, a whole bunch of stuff about how to calculate it. There's an online dose calculator that has controversial dosing a equivalence for methadone, and fentanyl, and others. I'm sure pretty much every state has some mention of MED or MME somewhere or another. So it's often reported per time period, which is often daily, or else totaled over the whole study. So if it's a 5-day study, they may say over the whole 5-day period, here's the MED.

You can look at the dose prescribed and the number of pills given. This can be you've given a

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scheduled dose of medication or it can be as needed. Most prescription consumption, if you think about this in the chronic pain world, is in an unmonitored setting and being at home. And actually, in acute pain real life, it's outside of the hospital. It's not just that first period of time when you're in the hospital. Most of it is outside the hospital.

So it's hard to know what really happens when you give it to someone. Higher doses definitely are more risk for more adverse events. And more pills prescribed, or given, or distributed leads to more available for diversion and misuse by whomever.

That's a little bit of background, so now we'll talk about acute pain a bit. There was a recent review, which I thought was really pretty interesting and helpful, by Kumar, published 2017. It's an opioid-sparing review with a hyphen.

(Laughter.)

DR. STACEY: The review of studies demonstrated opioid sparing for adjuvant

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medications, regional anesthesia, and nerve blocks, and went through a bunch of studies showing opioid sparing. And by far, the most commonly reported outcome was reduced opioid consumption the first 24 to 48 hours, usually totaled MED/MME kind of thing. And that's how they determined there was an opioid-sparing effect.

I love their conclusion. "While individual pieces of optimal postoperative pain management plans have been studied, long-term outcome data are lacking, as well as data regarding rebound pain. There is much work to be done." I forgot to close the quote, but "There is much work to be done." Yes, and I think that's why we're here. There is much work to be done in this area.

So I thought I would look at a few studies, acute pain studies. These are not exhaustive because, as you heard from Shannon, there's 80 acute pain studies, which she was able to identify. There's a whole bunch, but here's one, which is a phase 3, multicenter, double-blind, placebo-controlled, randomized trial of a drug with a whole

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bunch of subjects, with everybody getting the exact same operation, the very well studied bunionectomy. Everybody loves that bunionectomy model.

All patients had standardized anesthetic approach and initial analgesia with a popliteal sciatic block and a metatarsal block. The study medication was not given until after the first day, interestingly, then they're randomized to different doses of the study drug, celecoxib or placebo. And they had a whole bunch of outcome measures: pain intensity difference; treatment groups; placebo; proportion of patients who used rescue; time to first use of rescue; number of tablets used.

So the results were the active treatment resulted in reductions are most pronounced after 24 hours and did not extend beyond the 48-hour period. So I had a lot of thoughts about this, which will come up as we look at these tables. So there's zero to 24 hours when there's no study drug being done; it's just the groups before they're given the study intervention. If you can at what the little tiny writing at the bottom says, it's the

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proportion of patients who received rescue medication in the first and second 24-hour period.

Basically, a lot of people got rescue medication before they got the study drug. They're given the study drug, and if you got placebo, it helped because pain subsides after a bunionectomy, after 24 hours. But it didn't help as much as the active treatments. That shows some opioid reduction there.

This one looks at the number of actual rescue medications that were given to the groups as a whole at the top, and then the groups by those who receded study medication. So it looks like it reduced your chance of getting a rescue drug more than if you're in any of the groups that got a rescue medication, and didn't necessarily reduce how many rescue meds it got in any meaningful way. So there's a study that report some opioid sparing. It stops at 48 hours. I don't know what they went home with after that.

Here's one that TJ could comment on a lot more than I am, but I'm going to still present it.

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This is a secondary outcome, so it's looking at two studies together for abdominal pelvic orthopedic surgery for an intervention with an active control and then a placebo, a whole bunch of subjects, 608 subjects. Intervention was the IV anti-inflammatory, a placebo dose adjusted by non-pain factors; several opioid assessments; proportion of patients requiring opioids; and cumulative opioid dose over the 5-day study period.

So multiple ways to look at the treatment groups getting less opioids were discovered in the end. This is a secondary paper, but a good one because it had some interesting information in it, so here we go. This basically shows compared to placebo, a lot fewer people required opioids. And if you look at the cumulative dose, it's less; so many ways of reporting this. This is a different way. And this is saying, hey, we collected a lot of data. Let's break it out separately and report it separately from the primary outcomes from the study. I think it's helpful.

This is a different environment. This is an

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emergency department, and this is emergency department treatment for patients with acute extremity pain. It's moderate to severe. It's enough that the patients are saying I need something for my pain, so they're going to give them something. And then the outcomes were assessed after 2 hours only. So remember, it's an emergency department, and we all remember that house of God phrase about this. But the goal is to get them better now, and then once they're better, now we're done.

What they showed is a significant reduction in pain in all groups. What they're really looking at was ibuprofen and acetaminophen together versus three different opioids dosing things, and showing the ibuprofen and acetaminophen together really was quite opioid sparing, if you look at this.

If you look at the morphine equivalence here for the ibuprofen and acetaminophen, really quite low, 1.6 versus 8.6, 6.7, 6.35 [indiscernible]. That is pretty darn significant, it seems to me, reduction. So basically a lot of those folks

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avoided opioids. I thought that was pretty interesting, and that's the first 2 hours. Back to the review article, was it rebound pain? I don't know. I don't know how it worked.

This one is looking at the duration of analgesia, which was assessed as kind of their first request for pain medication or pain score of 4 or -- moderate to severe range of pain. They had a whole bunch of measures looking at duration of analgesia and motor block, et Cetera, and basically showed that there was in the active treatment groups decreased opioid dosing, and patients were more satisfied with that decrease opioid dosing. So it's reported lots of different studies, lots of different ways.

Here's what I thought was quite a bit different. This is not a medication study. I'm trying to present a couple of non-medication studies. This is using an immersive virtual reality experience for patients undergoing painful wound care in the hospital for which they're getting IV fentanyl. So it's a big deal; it's a

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painful thing.

They put on the headset, the goggles, and they're in snow world. You guys know about snow world, which is a Seattle developed artificial world where people get distracted, and they have to manipulate things and move things around. So something can be done to the rest of them, and they don't notice it quite as much. This showed a slight reduction in opioid, not super dramatic, but they pretreated the patients with a pretty significant dose of fentanyl, so I think it made it much harder to show a significant effect.

If you've never seen it before, this is kind of what it looks like. They're looking at this little view of these things out there, and you do things in the world with what you're paying attention to. At the same time, there's a very medical experience happening on the rest of your body while you're wearing your goggles. So it's kind of a cool way of thinking about reducing opioid requirement and definitely different the typical medication experience.

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TJ talked a little about enhanced recovery after surgery programs, a while ago, it used to be preemptive analgesia and preventive analgesia, and then the term was multimodal analgesia, and now it's really more enhanced recovery after surgery for the most part, which my version of describing what that is, it's many interventions, a systematic, multifaceted team approach spanning the perioperative period with multiple objectives. Improved pain control is not the sole focus. The goal is to get the patients out of the hospital, keep them out of the hospital, and not have them come back, and recover faster. And somewhere in there is pain and opioids.

I looked at two recent reviews. The first is a meta-analysis. It talked about all sorts of outcomes and did not talk about opioid dosing in the meta-analysis. The second review had a prominent focus on opioids but didn't report really what they were looking at in the study that they were analyzing for deciding there's opioid reduction and opioid sparing. So not nearly as

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helpful, I said, "Yes. Look, there's opioid reduction in all these areas but doesn't really go into any details whatsoever." I'm not going to go into any more detail on this. TJ covered it a bit.

Then there's this whole issue about the opioids actually prescribed for surgery, and this kind of gets back to my initial vignette of the person who gets in desperation and is able to find dozens of opioid doses around the household. These are a whole host of studies that showed that a large proportion of medications prescribed in the acute perioperative period are never used, which means they hang out available for unmonitored use at some future date. And they've shown that persistent opioid use is just as likely after minor versus major surgeries, as we saw this morning. Then if you prescribe less, you still have happy patients.

So it is amazing to me how these opioid-reducing claiming studies don't look at the actual opioid prescriptions for the most part. These are studied like in separate areas. We

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should put them together potentially.

Now, I want to talk about chronic pain. There was a Cochrane review in 2017, handily, looking at interventions to reduce prescribed opioid use in chronic pain. They were able to identify 5 studies that the populations are quite heterogeneous, as were the interventions and the outcomes reported. And they decided what a responder was. They decided to look at responders. At least a 50 percent reduction in opioid consumption was part 1, or complete opioid withdrawal, or reduction below a high dose. So if your dose was above 120 MED, and you're reduced to now under 120 MED, that was considered to be a responder as well.

A responder also had to have, at worse, no increase in pain as a result of the intervention. Both aspects of improvement had to be maintained for at least 3 months post-intervention. So back to the question about how long does a study have to be? At least 3 months for this review. I looked through this, and, really, opioid use was not

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assessed in any kind of common way. It was really, really vague how it was assigned. And all the other outcomes, which we've addressed in every other IMMPACT meeting, were inconsistently reported.

My conclusion is nothing really helpful here. We can improve the literature really easily as a group by coming up with some studies here. My second conclusion is 50 percent reduction in opioid dosing is a pretty high bar. Is any reduction meaningful? Does it need to be 20 percent, 30 percent? It's a thing we should discuss, but 50 percent seems high, and we really think that IMMPACT guidelines should be used for outcomes.

They kind of go on to say, yeah, there's a lot of limitations, there's a lot of work to be done. You can read this at your leisure later. And it talks about the multiple other outcomes we've talked about a little bit, about mood, social functioning, personal role functioning, et cetera, as important to look at.

This is another review equally revealing of

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deficiencies. They identified 61 studies. They found quality was good in 3, fair in 13, and poor in 51. One of the good studies did not really have opioid reduction as a primary objective, so it's not so exciting; multiple limitations. And their conclusion was very low quality evidence suggested several types of interventions may be effective to reduce or discontinue long-term opioid therapy, and that pain, functional, and quality of life may improve with opioid dose reduction; really a strongly worded, powerful conclusion.

I thought I'd just look at a couple of random things, so this is looking at -- this is not really a clinical trial up front, but it is an intervention. This is from Pacific Northwest looking at education and policies, a double dose is better. That's my summary of what the name of the study is.

The Washington state guidelines basically came up with this new high-dose idea of 120 milliequivalents. It was before I lived in the state of Washington, so I have nothing to do with

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it. It was basically published in 2007 and became more or less law and regulations in 2010. This big cooperative group added additional initiatives in education for their providers. They also had providers who were contracted providers, who did not get the additional education information about opioid reduction.

What they did in this study was they compared the group that got not just the state regulation but also their internal education and policies and reinforcement of the state policies versus those that just got the state policies. That included quite a few patients, 16,653 for the group practice and 5,552 for the contracted people.

They looked at MED plus people who got excess drugs, and there was definitely greater reduction in the group that got the double-dose of education. So their own providers did a better job than those who are contracted. And this kind of shows the trends over time of the doses coming down. This is the percentage of patients getting high dose in this first study, in this first graph,

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and this is those, about the average dose, how it decreases.

So they're pretty close to each other at the beginning, then there's separation out. So this would imply that getting education is potentially an effective dose reducer.

MALE VOICE: [Inaudible - off mic].

DR. STACEY: Pain scores were not reported in any consistent way. That was not their goal.

Here's a review looking at interventions. For those of us who do procedures, we think procedures are fantastic. They just take away all the nociceptive input, and pain goes away. It melts away, and you don't need opioids anymore.

Basically there aren't any intervention studies for opioid reduction as the primary outcome for chronic pain. The data to support opioid reduction is, quote, "very limited," which I would say translates to nonexistent. The best thing of this paper is this, which you may not be able to digest really super fast, but it's the myriad of factors that may make it difficult to reduce the

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opioids in a chronic pain patient receiving interventions for pain treatment.

There are really a whole host of factors in there that might limit that, ranging from procedural factors. The study factor is not designed to do that; social, biologic, pharmacologic, psychological, and medical, a whole bunch of things associated with being on chronic opioids in the first place and then not being able to reduce the dose. That was a nice review.

Some conclusions. For acute pain, pain satisfaction and function outcomes will be discussed of course elsewhere in other IMMPACT things. Acute pain studies report a whole bunch of outcomes, but there are a lot of outcomes that may have meaning, but those that extend beyond the immediate post-op period are rarely reported, and we need to really encourage that, in my opinion.

Chronic pain MED is by far the most common reported variable. High-dose patients using MED is often reported as an additional complaint. Getting patients all the way to office is also a complaint,

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and there are many challenges to actually conducting a chronic pain study for opioid reduction and opioid sparing.

The unanswered central question is basically what opioid dose outcome must you have in order to say this is indeed opioid sparing for both acute pain and chronic pain? Because right now, anybody can claim it, as far as I can tell. You can just say, oh, we've reduced opioids because we had one of some random outcome that was good. So if we can define what we think it is for the opioid dosing that counts, then that would be a positive step forward.

I tried to finish a couple of minutes early, and I think I did. Any questions?

(Applause.)

DR. FARRAR: Brett, a great review of the topic and raising some very interesting points.

DR. RATHMELL: Name?

DR. FARRAR: I'm sorry. John Farrar, University of Pennsylvania. I'm forgetting who I am.

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You started off with a story, and that is the story that is very often presented at FDA hearings where opioids are being considered, "My son went to a party and took a dose of something and died." And my question to you is, would any of the things you mentioned in terms of opioid sparing have an influence on that? Because to me, honestly, it sounds like a procedure issue, which is you need to get the surgeons or the whoevers to write less opioid for them going home. And clearly, as Bob was saying earlier, if we get to zero before they go home, then that's a clear demarcation point, but otherwise, you get 20 pills and use 10, and you still have 10 in the cabinet.

DR. STACEY: I would say yes, which is -- I don't think Dr. Loeser would mind me telling this story because I'm sure he's shared it with several of you in the room. He had surgery. This is John D. Loeser, had surgery, a relatively minor -- not a big deal surgery. He received 120 tablets of a medication and used a handful of them, or less than a handful of them. So he had a whole bunch sitting

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around.

If instead he had been prescribed 15, that would make a big difference. If this person at the beginning of the story, his family had been prescribed 5 or 10 per episode, would not have been able to come up with dozens, and may not have come up with a dose that would have been potentially fatal.

So I think dose reduction in the unmonitored setting of not in the hospital is what really counts for reducing overdose tests. Because how many of you have done opioid trial? Raise your hand if you've participated in a trial of an opioid.

(Hands raised.)

DR. STACEY: How many of you have had an overdose death in that trial?

(No hands raised.)

DR. STACEY: Oh, so clinical trials never kill somebody. Drugs must be all safe if no one ever dies in the trial. Right? That's not true. So we need to do some extraction to the real world.

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DR. FARRAR: And I agree completely. My question, though, was not about writing less opioid. That doesn't strike me as opioid sparing. What that is a procedural process where we don't give too much opioid to people going home. When we're talking about opioid sparing, we're talking about reducing the amount that people take.

DR. STACEY: So the reason that John was able to go home is he got multimodal analgesia, and he had an effective multicomponent analgesic approach that led him to be able to take less opioids.

DR. FARRAR: But he went home with 120, and that's the issue that ultimately led to the death of the -- or the near death of the patient you were describing.

DR. STACEY: So I think the way to think about it is that we need to -- if we're part of the perioperative experience, we need to look beyond the discharge and think about I want to get the maximum for benefit for what I do that extends beyond. So there's that. And then also when we're

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doing refills in the chronic pain situation, think about chronic pain medications; think about that, too.

So that's not clinical trial stuff. That's not clinical trial stuff. If you reduce the need for the opioid, you can prescribe less, and the two have to go together. There's been a disconnect, now, with this, which there are various protocols that reduce the pain, reduce the drive, yet the prescription still stays up here. So that's less meaningful than if it's combined with the second part.

DR. RATHMELL: Just one more question.

DR. GROL-PROKOPCZYK: Hanna Grol-Prokopczyk, University of Buffalo. I'm still thinking about what opioid sparing means, as it seems most of us are. And now I'm thinking it's not just that one component or one parallel concept is reducing adverse effects. But based on your comment, there's reducing the dosage that people actually take and ingest, and then there's reducing the dosage that's prescribed. And the additive

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difference between those two is what's leading to the pills in the cabinet that people can get.
So maybe it's worth thinking about -- I don't know if a clinical trial is designed to address the amount of prescribed independent of the amount used, but that's something as a health policy issue should be addressed.
DR. RATHMELL: What we've seen is dozens and dozens and dozens of trials in an incredibly short period of time trying to define how many pills do you need after X, Y, or Z surgery. And that's actually happened. That's happened wholesale across the United States, is a reduction in prescribed, tailored much closer to what patients actually need for a given procedure.
DR. STACEY: All within the last 5 years.
DR. RATHMELL: Yeah, very, very short timeframe where all that's come out. And it's the surgical colleagues that have done most of that work.
Thank you, Brett.
DR. STACEY: Thanks.

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(Applause.)
DR. RATHMELL: Next is Srinivasa Raja. Dr. Raja is a professor of anesthesiology in neurology and director of pain research at Johns Hopkins. And he's going to talk to us today about sparing of opioid related patient-reported side effects and symptoms.
Thanks, Srini.
Presentation - Srinivasa Raja
DR. RAJA: Thank you, Jim.
I see a little bit of that puzzled expression in Bob and Dennis' face because the title isn't exactly the same as what is in the agenda. There are two reasons for this, and two challenges that I faced. One was when you speak later in the afternoon, how do you come up with a presentation that doesn't duplicate what's been already said by these excellent speakers in the morning? The second challenge was after about four weeks of trying to prepare for this talk, I found myself challenged in trying to spend the next 30 minutes sounding semi-intelligent to this erudite

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audience.
So what I did was what my colleague Eric Strain did this morning, which is ask for some help from Mr. Google. So when I faced this challenge and asked Mr. Google what should I do under these conditions, the answer I got was, when you don't have a good answer to a question, change the question.
(Laughter.)
DR. RAJA: So that's some of what I'm going to be doing. The other, in defense of what Sharon was doing this morning in her presentation, she said she's going to be asking more questions rather than answering some of them, Google also defended her and had this advice. Asking the right question is often more important than giving the right answer. And this was defended by quoting Einstein, who said, "If I had an hour to solve a problem, I spend 55 minutes thinking about the problem and 5 minutes thinking about the solutions."
So what I'm gonna do in this presentation is be somewhat provocative, ask questions, use some

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reports in the literature, and try to provide some conceptual framework for this.
In 1978, I was doing my anesthesiology residency, and the big news at the University of Washington, the big news was the Lasker Award being shared by Sol Snyder, Hans Kosterlitz, and John Hughes for opioid receptors and enkephalins, a discovery of the receptors and the endogenous opioids. So it is ironic that 4 decades later, we're looking at the adverse effects of drugs working on these receptors.
We know that the receptors are ubiquitous. They are present in the central nervous system, the pulmonary system, the hepatobiliary system, cardiovascular, and endocrine systems, so it's not unusual or unexpected that there will be adverse effects. We're looking at the CNS effects, such as sites of brain or spinal cord for the analgesia, but we also know that the same CNS sites of actions, where opioid receptors are present, may also cause sedation, depression, change in cognition, and opioid-use disorder.

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The effects of these drugs at the other systems, other sites, results in these variety of adverse effects or off-target effects you can call it, such as sexual dysfunction, nausea, vomiting, constipation by the effects on the GI tract, immune system changes resulting in immunosuppression and infection; effects on the biliary tract causing biliary obstruction, or respiratory depression due to the effects on the CNS and pulmonary system, and QT prolongation from cardiovascular effects.

Another way of looking at the same adverse effect could be what are those opioid related adverse effects due to? Are these due to receptors at peripheral organs or is it due to sites on the central nervous system. For example, CNS effects could result in sedation, euphoria, or delirium. They can also cause respiratory depression and opioid-use disorders. And the peripheral sites of action can result in gastrointestinal side effects, genital urinary side effects, or endocrine side effects.

So one way of potentially conceptually

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thinking is maybe what is the site of action, where are the drugs working, and is it an adverse effects related to the peripheral site of action or central site of action.

We've already heard today that after surgery, one has adverse effects, and this is just one such example that maybe about 12 percent of side effects related to respiration, GI, or GU, and that this may be more in men versus women, particularly after GI surgeries. Similar types of incidence studies have shown that in chronic non-cancer pain patients, Randy Moore or Henry McQuay had this view, which looked at the adverse effects of chronic opioids. And here it seems that a little bit more of the GI effects and the CNS effects may be more prominent.

A more recent analysis of multiple trials show that the CNS effects of respiratory depression may be less than 1 percent; falls and fractures may be 1 to 2 percent. But what's more predominant after chronic use are the hormonal effects, the effects on sedation, sleep, and depression, which

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is more along the lines of 15 to 40 percent. So depending on how the systems are, how the drug is used, whether it be acute or whether for chronic use, the relative incidence of adverse effects may vary.

We've also heard that the adverse effects result in economic burden. In this case, just an example from post-surgical pain and giving just one adverse effects, which is postoperative ileus, that patients who got opioids or had ileus, the cost went up, but doubled compared to those who did not have it.

Another way of looking at these adverse effects is maybe looking at the temporal relationship of when the drug was given and when the adverse effect occurred. For example, opioids given for acute pain, there are some immediate effects, such as respiratory depression and CNS sedation. This may occur within minutes to hours. There may be some intermediate effects that may occur over days, such as changes in immune function resulting an infection or delirium resulting in

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delayed functional recovery, or the more delayed effects such as susceptibility to opioid-use disorder.

Depending on when these occur, your outcome measures or metrics that you may use may change. For example, for the immediate effects, you may look at perioperative morbidity or mortality. If it's an intermediate effect, you may look at infection rates or progression of cancer in patients with cancer. For the delayed effects, you're more interested in the opioid-use disorder incidence or drug related deaths.

The same scenario can be made for use of opioids for chronic pain, and again can be thought of as immediate, intermediate, or delayed effects. And similarly, based on which effect you're looking at, again, the metrics or the outcome measure may be different. For example, for the intermediate, you could look at infection rate or sexual dysfunction or depression or suicide. For the delayed effects, the incidence opioid-use disorders or drug related deaths.

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The reason for that is the temporal relationship of the adverse event to the opioid use will dictate what should be the metrics that we use. It should be direct measures. Are they more surrogate measures? What are the sources of data that you may want to look at to examine these adverse effects and what type of data you would use. It will give you an estimate of what is the frequency of the event, and therefore what are the number of patients that you may have to recruit and when you collect the data.

I happen to, in this case, agree with Bob that I thought we would not have these 50-plus experts sitting in one field if the delayed effects, the opioid-use disorders and mortality, were the primary. So I'm going to focus my presentation a bit more towards those two adverse effects.

We've already heard from Eric this morning, and we are all familiar with the data on the increased use of opioids and the increased mortality. But what I did was a PubMed search on

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opioid sparing and pain over the last decade and found this interesting graph, which shows that over the last 4 or 5 years, there's a dramatic increase in the number of publications, which have the term "opioid sparing."

So then I asked the question what prompted this increase in reports in the literature of opioid sparing? I came up with this assumption that opioid use associated adverse effects and deaths are dose related; that opioid sparing can reduce opioid adverse effects, which in turn may reduce the opioid-use disorder and maybe opioid related deaths.

So the questions I then tried to answer, looking at the literature, were it is the evidence of relationships between dose and adverse effects; what strategies can be used or can help us assess if opioid sparing will result in decrease in the adverse effects, particularly opioid-use disorders and opioid related deaths; and how do we determine what is meaningful sparing of opioids that could lead to a clinical decrease in adverse effects?

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So what I'm gonna do in the next few slides is present some reports in the literature and see whether we can determine this relationship between opioid sparing and opioid adverse effects if it is dose related. And if so, does that result in reduction in opioid-use disorder and opioid deaths.

Let's start with this study, which just looked at all patients admitted to the hospital in a Denver academic center, over 6,600 patients. And they looked at patients who were described as opioid naive based on not having any prescriptions for opioids in the year before the admission. So prior to their hospitalization, they had not used opioids at least for 12 months, and then looked at over the next year how many of these patients were using opioids.

They had two groups; 25 percent of the patients got a prescription of opioids when they were discharged; 75 percent did not get a prescription for opioids. And the majority, as you can suspect, the patients who got the opioids were surgical patients, about two-thirds of them, and

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some of them had chronic pain. And then when they looked at the use of opioids, a year later, chronic opioid use in the patients who got a prescription for opioids at the time of discharge had an odds ratio of being more than 3 times likely that in the next year they'll continue to have a script. So at least they would have received a script for opioids one year after the discharge.

The other thing they looked at this is, was there a difference between those who were discharged after a surgical admission versus a nonsurgical admission, and they found that in patients who were admitted for nonsurgical indications, the odds ratio is almost double that for surgical admission. So I think here is an opportunity where we have a less well studied, high-risk group of patients to look at. So patients admitted to the hospital for nonsurgical indications may even be a higher risk than surgical indications.

There are limitations of this kind of studies. These are retrospective cohort studies.

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It looks at opioid prescriptions, in this case from a single pharmacy that these patients are sent to. All that we know is they got a prescription. We don't know how they used it, whether this is an opioid-use disorder, did they misuse a prescription, did they abuse it, did they divert it. We don't know that from this particular study.

So we have a lot of studies that are in the literature in recent years that have focused on postoperative patients and what happens in opioid-naive patients when they are discharged. Here are two studies, one of which was shown by TJ Gan this morning. The one from the left is from Stanford, the right is from Michigan. And again, they looked at large databases, in one case or 600,000 patients undergoing surgery over a 2-year period, and the other about 36,000 patients. They said opioid naive means no prescription for opioids in a 12-month period prior to surgery. Then they looked at 12 months post surgery, looking at what they defined as chronic opioid use.

This was a variety of surgical indications.

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The Stanford group said there were 0.5 percent ranging from .12 to 1.4 percent. On average, about 0.5 percent were considered as chronic opioid use. The Michigan group said it was 5.9 to 6.5 percent. So again, we can see there's a tenfold difference between these two studies. And what causes this tenfold difference?

The answer I think is, is what is the outcome measure that these two studies used? The first question, you can say that maybe the incidences are different because the type of surgery is very different in these cases. I then took two identical surgeries, laparoscopic appendectomy, laparoscopic cholecystectomy, which were in both groups. And again, if you look at the data, there was a 15 to 25-fold difference between the incidence of chronic opioid use between these two studies.

So what's the difference? The difference is this. In the right study in Michigan, they said any opioid prescription, 90 days to 180 days after surgery meant chronic opioid use. If they had a

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prescription within 90 to 180 days after the surgery, that was chronic opioid use. The left one was much more conservative, and they said 120 days supply in the 90 to 12-month period or greater than 10 scripts during the 1-year period. So you can see these two outcome measures are very different, resulting in very different proportion of patients who are considered chronic opioid users.

The questions that you can ask and came to my mind as well is which outcome measure is more reflective of opioid-use disorder? Filling the prescription, does that mean they are misusing, abusing, or diverting the opioids? Is there any relationship to the postoperative opioid dose that these patients were given, the scripts that they were given? And these were not studied in this or if they were studied [indiscernible]. And is opioid sparing likely to change this incidence? So do we have any data based on that?

Just about a week ago, I came across this study that was from actually the Harvard group. It was published in BMJ. And they looked at a large

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database, the Aetna database consisting of 37.6 million patients. And about a million of those patients had surgery over a 8-year period, 2008 to '16. And they used CPT codes to indicate that these patients had surgery.

In those million patients, they also looked for ICD codes for opioid dependence, opioid abuse, or overdose. They picked up a number of ICD codes, which will be reflective of dependence abuser or overdose. And they observed that 57,00 had received postoperative opioids. So 56 percent of these patients who had surgery had postoperative opioids. And of those, close to 6,000 had an abuse code in the subsequent period.

What that says is what one could think of as 0.6 percent of all surgical patients had an abuse code or maybe 1 percent of those who received opioids had an abuse code. This was about a 2.7 year after their surgery. They also looked at a variety of things. It was over an 8-year period, and they found that males, particularly in the 15 to 24 age group, had a higher incidence of this

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misuse diagnosis.

The next question that's the most important question and the most relevant question for our discussion is, is there an association between this misuse and the dosage that was prescribed to these patients? When they looked across the dosages, the slope of that line is fairly flat. Although there is some correlation, it says that an increment of 10 morphine equivalence only increases the hazard by about 0.8 percent. So the relationship between dose increments and the misuse diagnosis was fairly weak.

So reducing dose of opioids in the prescription, daily doses of opioids, may have a weak effect on lowering opioid-use disorder. So the question is, is there some other relevant, useful indicators? And obviously, I wouldn't be presenting this paper unless I thought there was something relevant, and that is this. If they looked at the correlation, the slope, it's a much better slope of the duration of the initial use after this surgery in terms of the misuse rate.

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What this suggests is that the duration of prescription rather than the dosage is much more strongly associated with the ultimate diagnosis of misuse. Obviously again, this is administrative data, so that's a limitation. One could say this is an underestimate because maybe the miscoding of abuse may be an underestimation. And opioid use, this is, again, scripts that were filled, and that doesn't mean were they using it appropriately and what happened; is this misuse, abuse, or diversion?

Until recently, a week ago, I was an optimist. I felt a good, well orchestrated preoperative opioid-sparing strategy will have a major effect on the opioid crisis. However, I'm starting to feel more pessimistic, and I think the problem is much more challenging and complex than what we think is.

Why do I say that? I'll give you a couple of examples of why I think this is more complex. Here again, we heard from a couple of speakers talking about postoperative or perioperative use of opioids and how the ERAS or enhanced recovery

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program may be a good way of opioid sparing.

Here is an excellent study from the UCLA group. They looked at a 12-month period when they initiated the ERAS program. And you can see in the left half, they've shown a dramatic reduction in the perioperative use of opioids, which are persisted in the next 12-month period. So this is kind of the introduction of the program and the subsequent program.

Then they looked at what happened to these patients when they were discharged home, and the prescription of the opioids were fairly similar across the 24-month period, again, reemphasizing opioid prescription at hospital discharge may have no relationship to what happened in the interoperative period. So opioid sparing in hospital may not decrease opioid prescriptions at discharge.

Another cause for pessimism for me was, again, the Brat study from the Harvard group, which looked at a number of different specialties and their behavior over the course of the next several

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years. And you can see trends, a number of specialties such as general surgery had decreasing opioid use post-surgery in the several year period. But when you look at the right in terms of relationship between the duration of use and the misuse diagnosis, that remained constant.

There doesn't seem to be a significant -- although the prescription opioid decreased, it didn't seem to reflect in the relationship between duration of use and the misuse diagnosis, again suggesting that maybe just the dose of opioid that they were discharge with is not the most important factor.

So despite mean opioid dose reduction -- and the dose reduction varied from 4 to 24 percent; even 20 percent reduction, there was no relationship or change in relationship between that and misuse. So again, you can say that the ICD code is underestimation, and maybe patient-reported outcome measures are more important.

We shouldn't be surprised with this because when you look at PK levels, the dose of oxycodone

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correlates very well. It's in 20, 40 and 80 milligrams. The peak plasma concentrations are linear. But when we look at things like drug liking behavior, there is a saturation effect. It seems like between 20 and 40, there is a change, but between 40 and 80, the liking behavior doesn't change.

So the question you can ask as if I reduce or spare the opioid from 80 milligrams a day to 40 milligrams a day of oxycodone, am I going to change the opioid-use behavior in the perioperative period or in chronic use? So this again raises the question, what dose is required to change this liking behavior associated with opioids? And we don't know the answer for that. It's definitely not a linear relationship.

So there are a number of patient-reported safety measures of opioids: abused safety efficacy, a nice review. Nine of these instruments are being studied. Some of them look at the global effect of safety, efficacy, and misuse, some a single measure of constipation; others of just misuse.

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So depending on what you're focusing on, a number of these measures that are available. Unfortunately, this review concluded that the clinical utility of these measures are equivocal, that some of these measures are not really feasible in clinical practice because they are either too long or too challenging. Some of them require trained observers and need to be further validated measures.

There are some measures available, which look at risk of aberrant behaviors, but if you're looking at the intent of the aberrant behavior, whether it is misuse, abuse, or diversion, there are only two measures that I'm aware of that specifically looks at that. And this was a focus of one of the ACTTION meetings in 2013. It took about four years for that paper to come out. It was published by Shannon as the first author last year. And they compared two main measures, the self-reported misuse, abuse, and diversion instrument, or SR-MADs, and MADDERS, which is the other measure, which Nat Katz was much involved in.

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There are differences between these measures. Again, SR-MAD is a 15-item measure, self-reported, used primarily for prospective use. And it maintains the anonymity of the patient and is also easy to use. It has some content validation in terms of patients with chronic pain. It's a qualitative study. But the construct and the predictive validity have not been done..

In contrast, MADDERS can be used prospectively as well as retrospectively. It is a little complex in the sense it's triggered by either self-report of adverse events or by drug accountability discrepancies, followed by an interview of intent, and then additional data that's available during the clinical trial.

So it depends on which context you're going to be using this. If you're using it in large-scale studies which may be needed for opioid-use disorders or opioid related deaths because of the small incidence of those, then you may have to use a scale that's easy to use. However, in the context of smaller clinical trials,

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MADDERS might be much more practical or usable. So I think these two measures still need further validation in terms of their sensitivity and specificity, but what measure you use will depend on the context of the study.

The last couple of slides, if you think opioid-use disorders was challenging, how about deaths related to opioids? The first study, this kind of dose related event of death and chronic pain patients using opioids came from the VA health data, which categorized patients on chronic opioids into buckets of no opioids, 1 to 20 milligrams; 20 to 50; 50 to 100; more than 100 in a broad group of patients, different categories.

They said whether it be a chronic non-cancer pain patient, a cancer diagnosis, or acute pain diagnosis, overdose related deaths was dose related. For example, for chronic non-cancer pain, if you use 1 to 20 milligrams, the death rate per 100,000-person months was .11 and 20 to 50 was .24.

So it gives you a little bit of what should be your sample size to be able to show differences,

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but this uses buckets, which are fairly broad, 20, 30, 50-milligram differences. So the question is, what is going to be important?

The same group, because they were unhappy with categorizing these patients into buckets, they then did a subsequent study where they had a nested case control with matching, looking at patients who died and patients who didn't die with different opioids. And they did find patients died after chronic opioids at a higher dose, but they could not determine a clear-cut point in the opioid dosage to distinguish between those who had overdose cases or those who died of overdose and the controls. So we don't have a clear-cut point of where there's a differentiation.

Then the lowering of recommended dosage, what they concluded was if they lowered it less than 100 morphine equivalence, it only affected a few patients that were not at risk, but maybe many patients were at risk. So that tells us that you may be wanting to -- if you're going to design a study, you may need to include those patients at

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higher risk and not ignore those patients.

Finally, anesthesiologists using these ERAS programs have said that we have an old way of treating patients in the perioperative period, where opioids were at the bottom of this pyramid, and now they should move up to the top of the permit. I think this is one way of looking at it. But I rather think that this should be actually a team effort where it's not just the anesthesiologists, but a whole group of individuals working to determine not just perioperative immediate use, but the longer-term use.

To conclude, the points I would like to make is in acute pain management, the acute adverse effects, the immediate effects, may be dose related. And in those cases, opioid sparing may be beneficial. But perioperative opioid sparing just in the immediate perioperative period does not necessarily equate to lower prescription at discharge, and that needs to be looked at as well.

In chronic opioid use in opioid-naive patients, we need to focus on how long these

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opioids are used; that is the duration of therapy post-surgery is important more than the dose of the opioid, that the patient-reported measures to detect misuse, abuse, and related events need further validation to test their sensitivity and specificity. And we have little quantitative data at this stage as to how much of a reduction in opioid dose will lead to a meaningful reduction in opioid-use disorder or in death. Thank you very much.

(Applause.)

MALE VOICE: Thank you. You've made us all pessimists.

DR. RATHMELL: We're all pessimists now. Okay, let's go home.

We're a bit over time. I'm going to respect the break. There will be plenty of time at the end. We're going to have all of the panelists for an hour at the end, so there's plenty of time for questions. I know you probably all have them. So back here promptly at half past the hour.

(Whereupon, at 3:05 p.m., a recess was

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taken.)

DR. RATHMELL: We'll go ahead and get started again.

Next on the docket, Dr. Ward, Denham Ward. He's professor emeritus in the Department of Anesthesiology and Biomedical Engineering at the University of Rochester, and he's going to talk to us today about opioid sparing relative to respiratory depression.

Denim, thanks.

Presentation - Denham Ward

DR. WARD: We've heard a little bit about respiratory in passing, so now I'm going to focus on the respiratory. I'm a big believer in experiential education, if you're going to remember things. So we're going to start out with a couple of little experiments here. This isn't a contest, but I want all of you to put your hands up. Take a deep breath out and hold as long as you can. When you have to breathe in, put your hand down.

(Audience participation.)

DR. WARD: A lot of type A people here.

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Okay. That was a little demonstration of the voluntary control of breathing and the chemosensitive control breathing. You have voluntary control over your breathing to a certain extent, and then your autonomic chemoreceptors are going to kick in and say, "I don't care if you don't want to breathe; you're going to breathe."

So it was two parts of the respiratory system that you just demonstrated. And I want to demonstrate a third part that's probably a little bit better exercise than the first one. I want everybody to close your eyes, take a slow deep breath in, hold it for just a second, and then take a slow, deep breath out. And when you finished exhaling, open your eyes.

(Audience participation.)

DR. WARD: So now that you all feel more relaxed after that little breathing exercise, you see a connection between your breathing and your limbic system; how your breathing can actually affect how you feel. So the brain has a lot of effects on breathing through a variety of systems.

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Quick disclosures, I do some consulting with some drug companies once in a while. What I'm going to try to cover initially is how we measure respiratory depression by opioids, both in the laboratory where we measure end-tidal CO2 and decrease in ventilation in the hypercapnic ventilatory response, HCVR, and the hypoxic ventilatory response, HVR, and clinically how we perhaps use saturation end-tidal CO2 and ventilatory arrhythmias; but then some complications on how we would develop study designs that include things like sedation, sleep, and concurrent pain that may affect our breathing.

Then I want to go through some examples, and I've divided it up into opioid sparing, in spite of all the discussion we've had about what really is opioid sparing, and opioids plus peripheral analgesics such as the NSAIDs; opioids plus central sedatives, traditionally like the central antipsychotics, anti-nausea vomiting medicines; and opioids in the new central analgesics, things like dexmedetomidine, pregabalin, and ketamine. And

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finally, I'm going to throw out some recommendations, I guess with my recommendations for recommendations so it can be then modified by the group.

Fred Plum I think had one of the best definitions talking about breathing being independently controlled. Breathing is the only coordinated skeletal muscle act that continuously fulfills, seamlessly integrates continuous metabolic and intermittent behavioral functions without normally disrupting the efficiency of either in the process; exactly what I'm doing right now. I'm breathing and talking -- besides talking and chewing gum at the same time, I manage to breathe and talk at the same time. And if you measure my arterial CO2, it would actually be normal. I'm able to integrate voluntary and involuntary seamlessly.

Traditionally, back in medical school, we were probably taught things like the chemoreceptors. We were taught that there were brainstem respiratory centers in the medulla and

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pons, and they went down the phrenic nerve to the diaphragm that controlled the lung function. And then there were central chemoreceptors and carotid bodies that measure the PCO2 and measure the PO2. And then on the right-hand side, upper panel there, you can see if you increase the CO2, you get a pretty linear increase in ventilation, a typical slope of 2.5 milliliters per minute per millimeter of mercury of CO2.

So if you end up with a CO2 of about 50, ventilation is up to around 30. I can point it out here, but not everyone in the back can see the pointer, and it's hard from this angle. But a CO2 of 50 ends up with a ventilation of about 35 or 40 liters a minute, about 4 or 5 times normal.

We sometimes see patients in the recovery room, recovering from anesthesia with a CO2 of 50, and we don't really think too much of that. But if I give any of you a CO2 of 50 millimeters of mercury to breathe, you're going to be breathing at about 40 liters a minute. Similarly, with desaturation, which is a linear decrease with the

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saturation -- the lower panel there shows it with a desaturation of about 80 percent -- the ventilation is up around 20, 15 or 20 liters a minute. Those are both graphs from my lab from individual volunteers.

But it's really more complex than that. It's not just that nice little -- as we demonstrated with our little exercises that we did, the chemoreceptors is only part of the whole control of breathing. We really have to take into account the cortex. The subcortical limbic system has a lot of effect on it, and then not just the chest wall with the upper airway obstructions, too, with really a much more coordinated system that the opioids are going to act upon than just that simple metabolic CO2 controller.

Functionally, it's much better to think about dividing a system up more like this, as 3 pathways that control our breathing. There's the traditional metabolic control. There's a CO2, O2 chemoreceptors, the carotid bodies, and the central medulla. But there's also a wakefulness drive.

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There's a behavioral control. Pain may come through that pathway. And there's a voluntary control. You can breathe. You can take a deep breath when and where you want to.

Normal resting is really a mixture of all three of these/ In different states, there are different effects. Normally resting, the first row there, probably is controlled mainly by behavioral and not CO2; maybe a little bit from CO2 and a little bit from voluntary, depending on what you're doing at the time.

Anaerobic exercise where you're generating a lot of hydrogen ion is clearly a metabolic control. For those of you who jog or run, once you get to about 20 liters a minute, you find you can't talk to the person that you're running beside because voluntary control is not going to be effective when that metabolic control from exercise has kicked in

REM sleep looks like more behavioral. There's actually not much response to CO2 on the REM sleep; REM sleep looks more like awake, as opposed to non-REM sleep, when you don't have,

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obviously, any voluntary control, the behavioral limbic system is suppressed by the non-REM sleep, and you're pretty much just under metabolic control.

Singing, talking, arousal, things like Ondine's curse and locked-in syndrome have their own effects. But what do opioids do? Opioids pretty much suppress metabolic control. Depending on the amount of sedation, it will suppress the wakefulness control. And it leaves the voluntary control more or less intact. Those of us who are anesthesiologists have often given a fair amount of opioid to a patient, so they've stopped breathing, and then just asked them to take a deep breath, and they surely will take a nice deep breath, a deep breath for us. The voluntary control will still be intact.

The one that surprises people, which I'm not quite sure why it should, because this was shown by Ray Fink many, many years ago, is the fact that normal resting ventilation is not really controlled by CO2. That still seems to be the dogma that's

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being taught most frequently. And what Ray did at Columbia in the early '60s, we took a group of volunteers who weren't physiologists and didn't really know that CO2 controlled breathing, and asked them to hyperventilate. And they hyperventilated down to CO2's in the low 20's, and then just said, okay, just breathe.

Now, if I asked you to do it, you'd probably stop breathing because you know if your CO2's only 20, you're not going to have any drive to breathe. None of these volunteers did. Their breathing kept right on at the level that it was. So here's the CO2. They hyperventilated themselves down to here. Here's after they stopped hyperventilating, and you see actually it was still up a little bit, and then stayed put. There was apneic period there.

So as Ray said, "Cerebral activity associated with wakefulness probably plays an important role in the maintenance of resting respiratory rhythm. Carbon dioxide appears to play a subsidiary part, and the main respiratory drive appears to be of neural origin."

Well, how about opioids? We've been talking about opioids and its effect on nausea, vomiting, constipation, all these other effects. Well, it also has a strong effect on breathing and one which we can quantify quite readily; a lot of different studies dating back to the 1940's. Santiago in 1979 had a nice paper because he combined the effects on both the hypoxic and hypercapnic effects, actually as well as exercise in the paper, too; 0.2 milligrams per kilo of morphine IM, a reasonable dose; ventilation decreased from 6.8 liters a minute to 5.1, with a decrease in both tidal volume and respiratory rate.

The lower left-hand panel there shows the hypercapnic response. So again, you can see as the CO2 was increased, ventilation went up a slope of 3.5 versus 1.8. It's probably more interesting to look at the ventilation at a CO2 of 50. So if you look at the upper curve at a CO2 of 50, the ventilation was about 50 liters a minute in this group of subjects. After morphine, the ventilation was about 20 liters a minute; so cut the

ventilation by over half at a CO2 of 50.

A similar effect with the hypoxic response on the right-hand side, you can see the increasing ventilation with the decreasing saturation, a normal response about half a liter a minute per 1 percent decrease in saturation. That was cut down to 0.16. And his example, it's also nice to look at what the ventilation would be at a saturation of say 70, which in the control was about 25 liters a minute. Oxygen is not as strong a stimulus to ventilation as CO2.

The combination is very strong. The asphyxial response of hypercapnia and hypoxia is the strongest response across. With a saturation of 70, ventilation went down from about 25 liters a minute, down to about 10 liters a minute; so a strong depression in both the hypoxic and hypercapnic response, more than what you would see at the resting level, I think what we would call a moderate dose of intramuscular morphine.

I can't talk about effects of opioids on respiration without the classic study by my mentor,

Jay Bellville, who was my mentor at UCLA, who looked at the effects of sleep plus morphine. Most of the studies that are done, you've got a subject awake, maybe a mouthpiece in their mouth, breathing on an apparatus, and you give them some morphine, and they're still awake.

What happens if they fall asleep? In a study in Anesthesiology with 4 subjects, that would never get published today, of course, showed a drastic reduction in both the slope and the absolute ventilation, compared to rest, compared to morphine, compared to morphine plus sleep. So curve over in the right-hand side of the hypercapnic response curves, the steeper one is actually the morphine one and the flattened one is morphine plus sleep for one individual subject. And if you care, you can see the 4 individual subjects, the data.

As Jay said, "How much of the very substantial respiratory depression seen during anesthesia is related to the altered state of consciousness and how much is due to the drug

per se?" Certainly this study poses many problems concerning the interaction of sleep, altered state of consciousness, and drug effects, because it's very difficult to associate out how much is just the drug itself that may be acting on the chemoreceptors and how much is acting on the cortical limbic systems by changing the mood, changing the affect, changing sleep, and changing sleep state. This study has only been reproduced once by, by Dick Neal, and that was about 25 years ago, finding the same thing. I'm not aware of it ever being done looking at REM versus non-REM sleep with opioids.

Now, I want to go through some examples. This is not a systematic review. It's not a scoping review. I just pulled out some papers that I thought had interesting methodology that were typical of the kind of methodology of the studies in these three areas: opioids plus peripheral, opioids plus central sedatives, and opioids plus central analgesics. And I've tried to divide them up both in volunteer studies that are done in the

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laboratory with perhaps a little more care about the data that's being collected on the respiration and clinical studies, mainly post-op acute pain type studies.

Moren back in 1997 looked at an NSAID on a double-blind, randomized crossover study, looked at ketoprofen, morphine, and then the combination of the two of them. Now, one thing commonly you see in these studies is the combination uses the same dose that they started out with the individual ones, so you've got some potentiation there, or not, but there's no effort to try to reduce the doses to get equal analgesic. And in fact, almost none of the laboratory studies have a good measure, if any, of any kind of analgesic effect.

Interestingly, they did measure the hypercapnic ventilatory response, and you can see on the graph there, the open circles is the NSAID, the slope. The close circles is the morphine, and the open squares is the combination. So they actually found the combination had less respiratory depression than morphine by themselves, indicating

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that the NSAID partially reversed the respiratory depression from morphine; an interesting result, not really duplicated in many of the other studies. They didn't do any analgesic effects.

Liu 1993, a lot of these are older studies because we did these studies when these drugs first came out often, and then kind of lost interest in what their respiratory, morphine-sparing effects would be. Liu in 1993 looked at post-op patients, double-blinded, placebo-controlled saline versus 60 milligrams of ketorolac given pre-op. So he gave IM ketorolac pre-op, and then looked at how much pain there was in the PACU by measuring the amount of fentanyl that they used.

They did find that there was less fentanyl used, and the patients reported less pain in the PACU. But the only thing they measured was some lung mechanics. They measured some FEV1's, one which hadn't changed. They had no measurements of any of the control of breathing effects, including saturation and end-tidal CO2, or any of the simple clinical measurements.

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There are a lot of case reports out there, and they're interesting. To illustrate the difficulties of the interactions, Jain and Shah back in '93 had a case report of respiratory depression following a combination of epidural, buprenorphine, and intramuscular ketorolac. They had a patient that had an epidural buprenorphine that was still having some pain; gave IM ketorolac, and the pain decreased, and they got a respiratory depression.

Pain is a wonderful anecdote to opioid respiratory depression. And if you take away the pain with another modality, then you don't count on the respiratory depression and you increase the respiratory depression, because the classic one for an anesthesiologist is the patient with a broken leg in the ED that gets a bunch of morphine to control the pain, you bring him in the operating room and put a spinal, and the pain goes away and they stop breathing because the respiratory depression from the opioid plus pain was not substantial. The respiratory depression from the

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opioid with no pain is very substantial.

So it becomes difficult -- if you're going to measure respiratory depression, you have to very carefully define the state of how much pain is involved, are they awake, are they asleep, and how much sedation is involved because these other things have a very strong effect on the respiratory system.

How about the central sedatives? When I was an intern back -- I won't say -- but back in the early '70s, mid-'70s, 50 of demoral -- horrible drug -- 50 drug, 50 of phenergan, that's at least as good as 100 of demerol.

Anybody else from my era remember that 50 of demerol, 50 of phenergan? That was what every post-op patient got. Well evidently, in the '70s, we hadn't read the literature because Arthur Keats back in 1960 looked at that -- and again, a paper that would struggle to be published today, but looked at both post-op patients and volunteers in the laboratory.

The post-op patients were not blinded or

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randomized, but looked at demerol 50 and phenergan 50, plus morphine, and in volunteers randomized looked at demerol 50 milligrams, demerol 100 milligrams, and demerol plus 50 and phenergan plus 50, and looked at the hypercapnic ventilatory response, and didn't find any effect. There was no increase in the analgesia. There was no increase in the respiratory depression. But they were a lot sleepier.

So he concluded the addition of promethazine to meperidine did not increase respiratory the depression, didn't increase the analgesia either, but markedly increased the sedative effects. So the 50 plus 50 really was not accomplishing anything as far as opioid sparing was concerned.

Sometimes you want to look for things. Olson 1986, in volunteers not blinded gave morphine .15 milligrams per kilogram and then randomized chlorpromazine, prochlorperazine, 12.5 milligrams versus saline. The morphine decreased the hypercapnic ventilatory response by about 40 percent and decreased the hypoxic ventilatory

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response by about 50 percent. That's the same data that we kind of saw in Santiago's study that I showed you before.

The prochlorperazine/chlorpromazine had no effect on the hypercapnic ventilatory response, but the hypoxic response was reversed. The hypoxic response was markedly increased almost back to the pre-morphine level. And that's known because the carotid bodies have a dopaminergic receptor in them, and plus the chlorpromazine is an anti-dopaminergic drug, so that increases the hypoxic response and counters the effect of morphine.

So if you're looking for a hypoxic response, the central sedative actually counters the depression of the hypoxic response. Again, he made no analgesic measurements, so he cannot make any statement about whether the chlorpromazine had any increase in the analgesia.

Probably the more interesting drugs today are the three central analgesics. Peter Bailey back in '91 looked at clonidine PO, morphine IM,

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and then the same doses of clonidine plus morphine and didn't find a whole lot of an effect. Look at the two curves down in the bottom. The left-hand curve is the slope and the right-hand curve is the ventilation at a CO2 of 50, which is probably the more interesting one to look at.

You see the clonidine in the top curve did cause some respiratory depression. The morphine caused some respiratory depression, and the two of them together were pretty much additive; so the amount of respiratory depression from each one of them, added together to get the bottom curve, which is the clonidine plus the morphine. So a little bit of respiratory depression with the clonidine and less change in the slope. The left-hand curve shows clonidine did not have much of a change in the slope -- that's the top curve -- but it did shift the curve over to right.

Lin, British Journal 2009, looks at dex. It's a clinical study, post-op, double-blind, randomized, looked at morphine and morphine plus dex via PCA, and showed a decrease in the amount of

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PCA morphine being used as a measure of the opioid sparing, significant even at the 1-hour level. And very typical of these studies -- and I could have found multiple ones -- was the quote, "There was no report of somnolence or respiratory depression in this study." The misspelling is mine, not his. If you don't look for it, you're not going to find it. Saying that there was no report or respiratory depression does not mean that there wasn't respiratory depression.

Mildh in 1998 looked at ketamine, again, in volunteers, double-blind, crossover, randomized, looking at fentanyl, 2 mgs per kilo, and fentanyl plus ketamine. Interestingly, if you look at the bottom curve there, the fentanyl plus ketamine is the upper curve and the fentanyl plus placebo is the bottom curve, and this is just the minute ventilation, the resting minute ventilation. And you can see the fentanyl reduced the resting minute ventilation from about 8 liters a minute down to 4 liters a minute, and that was counteracted by ketamine. So the ventilation went down but didn't

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go down anywhere near as much, and was a significant difference.

That was their main finding. But if you read the paper a little more carefully, there was a statement in there that pulse oximeter saturation decreased to 90 percent in both groups. So there was a decrease in saturation at rest, less than 90 percent, which a lot of us would put at the criteria which you'd want to have some sort of intervention, supplemental oxygen, even in the Ketamine plus fentanyl group. So the ketamine, while it did reverse some of hypoventilation, CO2 only went up to 6 as opposed to 10, it was still a decrease in saturation.

I wanted to show this because they illustrate there's a lot of things you can look at as far as what respiratory depression is after these drugs, and there's no consensus on exactly the right one to look at. And from the laboratory studies like the hypoxic ventilatory response and hypercapnic ventilatory response, there's not solid data, okay, if you're hypercapnic, your ventilatory

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response is reduced by 50 percent; that puts you at high risk for respiratory depression when you use the drug clinically. That data does not does not exist. That's some hypothesis out there that that's true.

Michelet, British Journal in 2007, post-thoracotomy, which is an interesting use of the combination randomized control trial, pure morphine PCA versus morphine plus ketamine PCA. The left-hand panel there shows the decrease in morphine use as less PCA. And then they used one of the better, I think, outcome measurements for respiration in a clinical study.

They measure the amount of time with saturation less than 90 percent, also at 95 percent, but I used the 90 percent as perhaps a more clinically relevant number. That's probably when the intern would get called by the nurse, when the saturation got down below the 90 percent, so at least the intern on call probably cares about this one.

As you see in the left-hand panel, there was

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a decrease, which didn't become significant until the cumulative dose at 36 hours. But there was a substantial significant, both clinically and statistically significant decrease in the percent of time spent below 90 percent saturation in these post-thoracotomy patients. These are all lobectomies. They are open thoracotomies without any epidurals, so the amount of splinting and post-op pain is pretty substantial in these cases.

So there was still some time less than 90 percent saturation, but it was substantially reduced by the combination of morphine plus ketamine. So is this a true opioid-sparing effect, then? You use less opioids and you had decrease in the respiratory depression, at least measured by the saturation in the post-op period.

Finally, a pretty new study, Myhre in Anesthesiology in volunteers, randomized, double-blinded, crossover study, used a remifentanil infusion, and used it not just as a continuous infusion, but did it to a target effect concentration, a TCI, of 0.6, 0.12, 0.24 nanograms

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per milliliter, and then the remi plus pregabalin, 150 milligrams PO.

They did an analgesic study in the laboratory. So they did a cold pressor test, a lot of different kinds of pain, although that cold pressor test is the kind of pain stimulus you want to use for opioids. But if you look at the left-hand panel, he's got placebo, the top curve, plus pregabalin plus placebo, the second curve, which pregabalin did a little bit. Remember, that was just one dose, so that was pregabalin alone. so there was no remifentanil. So it decreased the pain score by visual analog scale a little bit by itself. And that should be the horizontal line across because there was no remifentanil being given.

Next curve down is the no pregabalin plus remifentanil, and you can see the decrease in the pain score as the target effect concentration of remifentanil goes up with a pain score of 70 to 80 at the placebo beginning control, and then down to less than 20 with 2.4. And the pregabalin shifted

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that curve.
If you look at it, you can see that the pain with pregabalin at 0.6, without pregabalin, you need 1.2 to get the same pain score. And for a pain score of 30, with pregabalin, you only needed 1.2 nanograms per milliliter. But without pregabalin, you needed 2.4 nanograms per milliliter. So really half the amount of effect site concentration that was needed with remifentanil with 150 milligrams of the pregabalin.
Over the right-hand side, you can see what they looked at as far as the respiratory effects. The problem of looking at just resting ventilation is the effect is divided up into two variables. They're divided up in the increase in CO2 and the decrease in ventilation, so it's a little hard to tease out. You may not see a significant effect because the effect is distributed over 2 variables.
Pregabalin alone had very little effect on ventilation end-tidal CO2. As you added increase effects of the remifentanil, we know it's potent respiratory depression, and you can see that the

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end-tidal CO2 for the high dose of remifentanil got up to almost 50 millimeters of mercury, and we know how big a stimulant that is. And there was more or less an additive effect of the pregabalin. In other words, there was a further increase in the end-tidal CO2, a further decrease in the ventilation.
So opioid sparing, yeah, because you have a lower dose, and opioid sparing on the respiratory effects because there's a pretty much straight line, linear dose response curve. If you used less opioid at 1.2 versus 2.4 TCI nanograms per milliliter, it has less respiratory effects. So it spared both the analgesia and spared the respiratory effects of it; one of the few studies in which you've got good respiratory measurements, and perhaps not great, but at least trying to make some solid analgesic measurements.
The recommendations that I can throw out there is that early studies done in volunteers in the laboratory really should include some of the better, more precise measurements, of respiratory

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function, the hypercapnic ventilatory response and maybe the hypoxic ventilatory response, with some assessment of analgesia, just doing the respiratory sparing effects by themselves, and should have a dose-response effect.
So you can do, as I showed in this last study, some comparison of where the dose is with the adjuvant and without the adjuvant in the same group of volunteers.
Acute pain, late clinical efficacy, you've got to at least be measuring continuous saturation and continuous pulse oximetry saturation and continuous end-tidal CO2 in the acute post-op period, and may need some special overnight monitoring in patients like sleep apneic patients who are at high risk for desaturations because of obstruction, which is affected by the opioids but wouldn't be picked up when you are trying to measure something, and they're awake, and they're breathing on the apparatus, and you're measuring the ventilation; or they're in the recovery room and the nurse is talking to them. But they get up

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on the floor, and now they fall asleep, and they don't have their CPAP machine on, and they're going to desaturate.
Chronic pain, I don't know. There's really no accepted methodology that I know of to measure respiratory effects in the chronic opioid user. I think if you've got a patient with things like sleep apnea, you can do home-based overnight sleep saturation studies pretty readily now. Measuring sleep saturations at home on a chronic pain patient I think would be the minimum that should be done, and maybe perhaps formal sleep studies also should be done with that.
So finally, I think Richards back in 1953 had a good description. "Breathing is a truly strange phenomenon of life, caught between the conscious and the unconscious, and peculiarly sensitive to both." Thank you.
(Applause.)
DR. RATHMELL: We'll take questions right at the end. We're just about there.
DR. WARD: Perfect.

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DR. RATHMELL: Thank you, Denham.
All right, John Markman, last but not least, and then we'll have a panel for plenty of question and answer time. John is professor of neurosurgery and neurology and director of the translational pain research program in the Department of Neurosurgery at the University of Rochester. And he's going to talk to us today about the patient improvements and group differences that would be clinically meaningful; so kind of get at that all elusive clinical meaningfulness.
Presentation - John Markman
DR. MARKMAN: First, I want to thank Bob and Dennis, Valorie and Shannon and Jen, and all the folks at IMMPACT and ACTTION. It's a particular honor to speak with this group, obviously, the most important minds probably in our field. So it's really an honor. It's a little daunting because Bob would send out the agenda about every 3 days.
(Laughter.)
DR. MARKMAN: This is sort of like the Rolling Stones opening up for The Partridge Family.

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(Laughter.)
DR. MARKMAN: I see this every day.
(Laughter.)
DR. MARKMAN: And now, just to make it a little worse, I got half the people here just killing my talk, giving brilliant talks on my topic. Shannon, with a brilliant encyclopedic analysis of literature; Brett covering, in a very cogent way, some analysis about the chronic pain trials; Nat of course fast forwarding us to July 27th and giving us the concluding paragraph of the paper in the first talk.
MALE VOICE: It's already written.
DR. MARKMAN: So there's a lot of pressure here, but I'm going to try. The good news is it's probably going to be a little shorter than it otherwise would have been, so that's the silver lining.
I'm going to talk about clinical meaningfulness. I think, as Raj said, when you get this invitation, you begin to really begin to marinate these questions. You'll see some of my

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patients here. These are some of my influences and our relationships.
Here's the premise for my presentation. It's really this. Obviously, as you've heard today, over and over again, there's an enormous amount of uncertainty about just who should be on long-term opioid therapy, so who should take off on this plane. But I think we've also come to appreciate that there's probably more uncertainty about how to land that plane once you've taken off, and where to land. And there are a lot of different ways or whether to land at all. So I think that not only are there questions about who to take off and when to take off, but there are even more questions about how to land. So there's a lot of uncertainty about opioid sparing.
So because so much of my talk was covered better than I could cover it, I'm going to show some home movies from my clinic. These are two patients I've seen over the last 6 days who made me think about this presentation. The woman on your left is kind of a refugee. She spent her life

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living in the Catskills, far east of where I live in western New York. She was getting older, and she had a very debilitating spinal syndrome. She basically has had this slow burning cauda equina syndrome
She had her hardware removed in around 2011, and her scoliotic deformity began to progress, and she's basically ringing out her cauda equina, her nerve roots, like a wet dish rag over the last 7 or 8 years. She was managed, I think quite expertly, in her native region in the Catskills, but as she lost function in her legs progressively, they looked like little stork legs, and over her bowel and her and her ability to stand, she basically capitulated and decided to move to Rochester, where her son who's sitting behind her lives.
So she was something of an opioid refugee, and this is not uncommon. It's interesting that I was actually one of the advanced visit she made to Rochester before she moved in with her son because she didn't want to move until she knew that she had her therapy buttoned up. She was on buprenorphine

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for her pain after being on other opioids for a long time and had very good relief. But she didn't feel comfortable making this move until she knew that she had a plan in place. So I met with her and her son several times before she actually made the move. And we're going to hear from her and what she thinks about clinical meaningfulness.

This other gentleman is a very successful entrepreneur in our city, owns a lot of real estate and other businesses, but he had an aortic dissection, and when he clotted off his aorta and his iliac arteries, you can see that he lost his right leg, lost a lot of tissue in his left leg, and he has chronic neuropathic pain from his dissection and the surgeries that ensued.

I think my take-home for listening to these videos and helping you think about these patients and how I approached this problem, it's really embedded in the context of patient stories. When you read clinical trials and you look at the data, in some ways, it's confusing and it's hard to interpret because it requires a lot of statistical

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knowledge, and it requires you to pay attention and understand the methods very deeply, as you've heard today.

But what it does in a way I think, which you don't get unless you hear these patient's stories, is it takes it out of context. So I want to take some of the important issues, which you've heard really clearly discussed, and hopefully put them in the context of the voices of these patients.

Now, let's hope the video works.

(Video played and transcribed.)

WOMAN: I obviously would love to have a straight spine, and be out of a wheelchair, and go back to doing things that I did when I wasn't. I have a fairly high pain threshold, I think.

MAN: I do, too.

WOMAN: When I say I need medication, I don't do that easily. It's not a stigma, but I just don't like medication, but I recognize I need it for some things that I'd be stupid not to take it. So I don't think anybody is arbitrarily saying to me, "Your dose is too high; reduce it," without

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being aware of my situation, as Steve said. It's the wrong question, and it's the wrong action.

DR. MARKMAN: So we had a discussion. I mentioned to her that I was coming to this meeting, and we were thinking about opioid sparing and whether she would consider lowering her dose, and how would we do it. And that's the video that sort of set up this discussion.

She had just had a flare of her pain, which she has these episodic flares. They last about 24 hours. She has them very infrequently. She has extraordinarily good pain control on buprenorphine. But she did have a flare, so she was particularly apprehensive about the thought of lowering her opioids. And some of the papers, which I'm gonna talk about, especially one by Mark Sullivan, I thought there were some really beautiful paragraphs talking about the apprehension and how that related to the clinical trial.

I think it's important also to understand why buprenorphine was used in this patient. I think it's particularly apropos given the talk we

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just heard by Dr. Ward, which is brilliant. Obviously, buprenorphine has these unique features, and I think one question I have in my own mind, buprenorphine has this attenuated effect on respiratory depression relative to other opioids, certainly relative fentanyl, and I'll show you a little slide about that. But the bottom line is whether that's an opioid-sparing strategy drug, which is a partial agonist and antagonist to a receptor of the opioid pathway. Is that an opioid-sparing therapy?

Dr. Fields and I were talking about that this morning over breakfast. As Dennis said, the beauty of this meeting is a lot of the intellectual ferment occurs in the breaks and over dinner, and I've changed my talk 4 times after breakfast.

This is a picture of her spine. Unfortunately, this was almost 11 years ago. Her spine is completely folded in on itself at this point. But just to give you a drama, that picture doesn't tell the whole story but just gives you a sense of the situation. And for those of you who

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don't practice every day, this is what you look at all day long. We don't look them in the eye anymore; we look at screens like this.

This is a screenshot from Epic, which is the electronic medical record. And this is the order form to order her buprenorphine. And you can see if you look closely here, inside this, there is a box there, which is in yellow, which has, "single dose at 24 milligram exceeds the recommended maximum, 16 milligrams" -- this is the dose she came to me on, actually -- "by over 50 percent," and I've got a couple of choices.

The first choice for override reason, is the benefit outweighs the risk. I usually choose this.

(Laughter.)

DR. MARKMAN: It seems like a good defense, right? But you've got about 6 others. When you're using the system all day long, you get a little paranoid. You think that immediately, Cellino and Barnes gets an immediate copy of anything you put in this box. They get a carbon copy. That's the personal injury firm in our region. And another

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one goes to the DEA, and then you press on this box, and you send the script off to the pharmacy because you just have this sense that it's all being monitored by some other third party that you don't fully understand.

But you get these warning messages all day long as you're writing opioids and taking care of patients because you want to live in a world where -- we're more and more in a world where 50 milligrams is magical, or 120, or 180, and it's a one-size-fits-all world. But this woman doesn't have a one-size-fits-all spine. You don't walk into the running store in America and only have a size 8 shoe or a medium sweater at the department store. It's just not the way it works. Right?

I mean, personalization is probably one of the calling cards of our system. And yet here, when you try and personalize her care for her particular situation, whether this is the right decision or wrong, or whether you think the benefit outweighs the risks, you're immediately getting these warning morning messages. And if I'm worried

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about it, and this is what I do, and I've been doing it for 20 years, then you can imagine someone -- this is why she's a refugee. This is why she's wandering around looking for someone to write her medication.

So I just threw this in just now because I was listening to Dr. Ward, and I've always loved this slide which basically looks at the risk of respiratory depression and the margin of safety of buprenorphine relative to fentanyl. And what you see here is the differential effect of buprenorphine on respiratory suppression relative to fentanyl. And you can see that fentanyl continues to drive down that liters per minute, where it doesn't really happen with buprenorphine. It kind of plateaus there.

Again, is this an opioid-sparing strategy? I don't know. We've heard from Dr. Katz earlier that there are all these endocrine effects of opioids, maybe the most important set of side effects. Some people would argue that buprenorphine does not agonize and affect the

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pituitary axis in the same way that other opioids do. On the other hand, I don't really know. I do check that routinely, but in her case, I don't know if I'm making her osteoporosis worse and making her curve worse by keeping her on opioids sometimes, but it certainly occurs to me.

So I think I want to begin with this simple point about relevance and clinical meaningfulness. Opioid sparing may only be clinically relevant if, as Dr. Hertz said, the risks of long-term opioid therapy outweigh the benefits. When you begin to think hard about opioid sparing is when the risks of it outweigh the benefits. Now, it's not always so easy to see. Obviously, I wouldn't click that button if I didn't think the benefits outweighed the risks. I wouldn't take that risk. It's also I think, as my breakfast conversation with Dr. Stacey made me apparently and abundantly clear, not really appropriate until non-opioid treatment options are exhausted.

So those are the two premises or the two first checks. You have to ask yourself. And then

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I guess -- as we've talked about a lot today, and it's an insight I've kind of had over the last couple of weeks, but it seems like I wasn't the only one -- that opioid sparing may not make sense if there's a loss of analgesia. And again, there are other reasons, which we've already talked about extensively about why opioid sparing may not make a lot of sense.

I'm not going to dwell on these core domains, which I thought a little bit about from the studies I looked at. Obviously, in all of these studies that look at opioid sparing, there's a focus on pain intensity and all the things that IMMPACT has focused on over the last 15 years and over 90 publications. There's obviously a lot of consideration of mood, and quality of life, and physical functioning. You heard Dr. Haythornthwaite talk about the negative affect of opioids.

But I think the focus of the opioid-sparing outcome domains that I think are really the core of this meeting that we have to really hash out are

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those related to dose reduction. Is there a magic number? Which it seems like there's not a lot of consensus that there is, but certainly that's been the primary endpoint of almost every study that's been done in this field. The primary is always the amount of opioid reduced that I've seen, or very commonly. Shannon showed you others that weren't, but many of them were.

Obviously, this other question about opioid side effects and which are the serious ones and which are the nuisances, as we heard earlier. So some of these are nuisances and some of them are fatal, and how do we rank those and how do we prioritize those? That's that top circle.

So I'm not going to fill in these circles. I had a little bit more on this, but I thought Dr. Raja did a fantastic job talking about, for example, in the upper-right circle, what the opioid side effect measures would be, and how they would compare, and what we understand about them, and all their measurement characteristics, so I'm going to skip that.

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I'm going to focus on this study, which I really liked because it taught me a lot. When you're doing a talk, you always have to pick the study that you're going to pull yourself into the topic with. I love Mark Sullivan's writing, so I decided to focus on this one after Shannon and I talked about it or corresponded about it.

This is a prescription opioid taper support for outpatients with chronic pain. What they set out to do is demonstrate the feasibility of a prescription opioid taper support intervention. This was patients who had listened to a 14-minute video about someone who'd come off opioids and felt better, and then when they would have this series of interactions with a physician's assistant, who is specifically trained by some of the principle investigators in this study. And they'd go through a series of visits. It really gave them state-of-the-art cognitive behavioral care and other interventions.

The study looked at 22 weeks of the active treatment -- at the 22-week landmark analysis.

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They looked at mean reduction in opioid dose, and it was 43 milligrams lower in this opioid taper group than it was in the folks who were in the as-usual care. Now, this wasn't statistically significant. The author said, "The difference observed between groups in our study are clinically meaningful." As Shannon pointed out, no reference. Bit Mark Sullivan is like a philosopher king. Do you know what I'm saying? He doesn't need a reference.

(Laughter.)

DR. MARKMAN: I mean, he just laid it out, right? I was like, "Okay." I mean, it's good enough for Mark; 43 sounds good. It's manifest. I think we're done. And it's curiously close to number 42. For those of you who ever read the Hitchhiker's Guide to the Universe, where the answer for the whole meaning of the universe is 42, I thought that was curious. I mean, I wondered if he rounded up or something like that.

(Laughter.)

DR. MARKMAN: So was this study instructive?

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What did I learn from reading this study? Patients randomized to taper support intervention had a lower pain interference score. They had higher self efficacy for managing pain at both 22 and 34 weeks. They did well, and they harnessed all these nonpharmacologic tools, and they reduced their opioid related psychosocial problems. They had more interest in their usual activities, these so-called emotional hijacking that goes on with high-dose opioids. They had less trouble concentrating. They felt less down and sluggish.

It's something, when you put patients on buprenorphine, it's obvious immediately that that aspect of some of those opioid toxicities kind of goes away. Again, we were talking about that this morning. It's one of the most vivid things as a clinician that you see when you put a patient on buprenorphine.

It showed the benefits, with the opioid dose reduced, that patients did not have a significant increase in pain severity. So there wasn't that trade-off that we talked about where they had lower

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opioids but they were somehow writhing in pain. No, they had lower opioids and they had less pain. So all good. Who could argue with this? And there was no difference in the levels of opioid misuse, depressive symptoms, or opioid controls concerns.

But this is the part that really didn't sit well with me. This was called a feasibility study. The whole point of this study was to show feasibility. And I'm not a great math person. The primary barrier to feasibility in this intervention was recruiting and enrolling patients. It took 3 years to recruit 35 patients who were randomized, so basically a little under 1 patient a month. I'm not great at math, but that's a problem. A lot of us see 35 patients a day, so that's an issue.

What went on there, and why did it work out that way? They only enrolled 35 of the 144 patients who were referred to them. Only 72 percent of the patients went to most of the sessions, but basically they're enrolling about fewer than 1 patient a month, somewhere right around 1 a month.

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So excluded patients with current substance-use disorders, but allowed past substance-use disorders. I always think I never understand this idea. It seems to me that those are the patients who we're most concerned about here. That's the most clinically relevant population. In some sense, those seem to me like the patients who are more likely to die. They're more likely to have opioid problems. They're more likely to have -- what Dr. Strain talked about. They're more likely to give their opioids to someone else in exchange for something else and cause that societal burden. Why are we excluding them?

The study didn't use buprenorphine. For me, buprenorphine has been a godsend in my practice. I could never successfully taper patients off very high doses to low doses. It took too long and was too hard. You'll hear another study, which a debunks or counters that notion. But it was a very hard, laborious thing to get patients off opioids. With buprenorphine, you can land the plane in no

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time. It's like a Harrier jet. You can just get them right down.

Now, whether that's really just opioid rotation and not opioid sparing, I think that's a debate which is legitimate we could certainly have. But this study had more important limitations. It was unblinded, it was underpowered, and it was done by a single provider. So I don't know if this is feasibility in my book.

So let's talk about the clinical importance embedded in clinical context. This is this notion I want to put to you that you really can't really talk about meaning and significance, at least with inpatient, until you really hear the story.

(Video played and transcribed.)

MAN: Yeah, I fought hard not to increase my dose when was on there, but I did it because I didn't want to become more dependent on it and put more in my system. So I stayed, but I could see very easily to just get a relief to take more. It's addicting. It is addicting, and you kind of lose that edge because you build up a tolerance in

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your system.
DOC: Is your pain severe without pain medication.
MAN: Oh yeah.
DOC: And where do you have it?
MAN: Generally from my hip down.
DOC: And what does it feel like from the hip down?
MAN: Burning, pins and needles. You can't function.
DOC: You have in your phantom as well as in your --
MAN: On your phantoms once in a while. I get a big tingle, like a big twitch once in a while in my -- where my right leg used to be.
DR. MARKMAN: One thing I want to just take away from that, I think patients are always -- many patients but not all. And again, I think that one of the things that Eric's lectures have taught me over the years is that the cardinal feature of opioid-use disorder is loss of control. This is a story which I often hear, which is kind of the

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opposite to me. This is someone who's doing their own opioid sparing thing in his head all the time. He said I'm trying not to increase my dose.
I hear that all day long, and especially now. But even 5 years ago, patients are constantly trying to do their own opioid sparing thing to minimize how much they're taking. And he tells you it's addictive. He tells you he gets euphoria, and he feels --
(Video played and transcribed.)
DOC: So is being on a lower dose important or is it more important not to have those ups and downs?
MAN: It's better not to have the ups and downs.
DOC: So the absolutely doesn't matter. If you were on 180 milligrams of OxyContin but didn't have those ups and downs, or 16 milligrams, or 10 milligrams of buprenorphine and didn't have those ups and downs, that would be better than being on half the amount of oxycodone or half the amount of buprenorphine. Is that what you're

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saying?
MAN: I don't know. When you -- I also think that some people, with the OxyContin, they keep on wanting more because that kind of gives them a euphoric kind of like -- I don't know, kind of gives you like a -- I don't know -- like a -- I will say a stone feeling.
DR. MARKMAN: So this issue, he's noticing the focus on dose escalation over time and tolerance. But he's also telling you the one thing we really haven't talked about much today is this idea of micro withdrawal and the hyperalgesia withdrawal. We heard a little bit about it before. But to what extent is that something important to look at? Rather than absolute dose, what about just those fluctuations?
So the happiness of most people we know is not ruined by great catastrophes or fatal errors, but by the repetition of slowly destructive little things. And obviously, this epidemic and the opioid crisis is marked not only by catastrophes and fatal errors, of course it is, but there are a

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lot of patients out there who, again, are tortured every day with these slowly destructive little things like intermittent withdrawal. And I think that's important to think about also and why that might be a clinically relevant endpoint.
You saw this study -- or this is a big review that was done in the Annals of Internal Medicine. Brett did a really nice job abstracting from this, and so did Shannon. Again, they had a filter. They asked two main questions. They asked about the effectiveness of strategies to reduce long-term opioid therapy.
They basically focus on all the things you'd expect them to focus on, so I won't even go into it. But they looked at 3,522 abstracts. They got it down to 67, and these people were very finicky. They only liked 3 of these studies. I mean, they really basically hated everything. I would never want to go out to eat with these people.
(Laughter.)
DR. MARKMAN: They liked 3 studies, the tiny ones. And they looked at all different kinds of

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stuff, interdisciplinary pain programs; buprenorphine assisted dose reduction; behavioral interventions; detoxification; ketamine; acupuncture; some other cognitive behavioral approaches; lidocaine infusions. They did the whole waterfront.

They came across -- what you've heard already, that some of this literature -- I like the word that Nat used, that opioid-sparing studies tend to be dosed centric. It's like one of these hallmarks of an opioid-sparing study is like how much did you take? So they looked at that in many of these studies.

One of the studies they liked quite a bit showed this reduction of 10.1 in the active treatment arm with CBT and mindfulness meditation as compared with usual care. But none, as you'll note here, were powered to detect clinically meaningful differences in opioid-dose reduction. They don't tell you how you know exactly what those clinically meaningful doses are, but they just tell you that none were powered for that. So again,

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it's uncertain.

This is the Cochrane review, which just underscores, as Brett told you, the fact that we don't really have a literature to rely on. This is why we're all together in this bunker.

(Laughter.)

DR. MARKMAN: We're here to sort this out, and we won't leave until we do it. So we're going to figure out what that number is. There are different ways to think about this. One way to think about it, as is kind of responder analysis where you will have this menu of different where you put together these different features into a little bit of a composite, I think. Obviously, Dr. Simon knows a lot about that and has done that in fibromyalgia. But I was thinking that a composite of some type might be one way to solve this, no worse pain, a little bit stable function, but a reduced dose. And that would be the sausage that we try and make here.

I just want to talk about this study. I learned about it this morning after breakfast from

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Dr. Fields, and I thought this was quite interesting. This is just a research note from JAMA Internal Medicine, and this is from the Stanford group. This is a totally different model than the one I gave you earlier. This is about not using a physician's assistant, but this is about a community-based clinic, a single clinic, partnering with a physician.

So there's a contract, which is renewed between the patient and the physician in this model. And they agreed to reduce the dose over 4 months. There are 2 steps a month; 110 patients were screened. And in contrast to the one you heard from the University of Washington, here you had 82 of 110 actually enrolling, so there was something very compelling about the way they made their offering. And again, it was this 5 percent reduction and then increased to 10 percent reduction per week between months 2 and 4.

They relied on -- I thought this was a very good feature. They looked at the prescription drug monitoring database in their state. They looked at

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your in-tox screens. So they were trying to a little bit get at that societal piece that Eric was talking about and all the potential adverse events that could occur with an opioid-sparing program at the societal level.

The primary endpoint of course here was the change in MEDD from baseline, and pain intensity was a secondary endpoint. So there are a couple limitations here. One is that 31 out of 82 patients dropped out, so there's clearly something about this method, which probably needs to be refined before it gets scaled. But the median baseline dose was quite high. I was struck by this; 288 milligrams, and the average patient had been on medication for 6 years.

The median dose was reduced to 150 milligrams. The likelihood of a greater than 50 percent dose reduction was not predicted by the starting dose, by the baseline pain intensity, by the years prescribed opioids, or any other psychosocial variable. So I was struck by that.

This is their conclusion, which I thought,

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again, flew in the face of what I told you earlier when I said I used to have a really hard time getting patients down off their high-dose opioids before buprenorphine. They said, "Our data challenged the common notions," held by myself and others, "that patients taking high-dose opioids, or that the duration of opioid dose predicts taper success."

So I thought this was a really interesting paper. It's just a research note. It's a very small addition, but I'm grateful to Dr. Fields for pointing it out to me.

For the dose-centric, which I think some of us are, or at least feel like this will be part of the equation here, there are different ways to think about this. But one of the things I'm struggling with is do we think about a patient who takes 6 Percocets intermittently and very strategically, differently from the patient who is on a round-the-clock opioid at 90 milligrams every day?

I think about them different clinically.

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Clinically, that means something very different to me. The patient who says I don't take it for 5 days; I never get withdrawal. But if I decide I want to go play squash, or garden, or take my kids on the boat, then I take 3. And again, I look at those patients differently, and I wonder if we will as well as a group.

Again, the question is how small is too small? "If you think you are too small to make a difference, try sleeping with a mosquito," a famous quote from the Dalai Lama.

Then I think here is one of the biggest questions that I think we have to sort out. And again, this has been said before, but I want to come back to it; what to do with the patient who comes to you on high-dose opioids who you want to taper, but who clearly has opioid-use disorder, who's clearly out of control or has a set of behaviors, which are distinctly unmanageable? So listen to this patient.

(Video played and transcribed.)

MAN: Whatever you can do; there's 21st century. It's got to be something out there that can help me.

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DOC: Okay. And again --

MAN: Somebody's got to help me. I mean, I tried so many -- nobody wants to help me, it seems like.

DOC: Why don't they want to help you?

MAN: Huh?

DOC: Why don't they want to help you?

MAN: I don't know. I think it's because of all the medication, everything that I was on before. They're just scared of it because of the New York state laws, and they just don't know how to help me. Let's put it that way. That's the way I feel, sir.

DOC: And what part of your body hurts?

MAN: Everything?

DOC: Your whole body.

MAN: My whole body. My whole body's in pain.

DOC: And this has been going on, remind me for how long?

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MAN: Since 1989.

DOC: And it started just out of the blue, all day, one day, right?

MAN: It just started -- I was working in a -- I was working on a doc, unloading trucks, and one day I just couldn't walk.

DOC: And all of a sudden.

MAN: And then all of a sudden -- and then I asked. They said because -- you know, I thought it was because of my heritage, because I'm half Spanish, I'm half Latin, and I'm asked Sicilian> I said, "Could it be that?" First they said it could be Lou Gehrig's. I've been through so much.

DOC: Do you have Lou Gehrig's?

MAN: No. I told you the doctor found out what I had was Dr. --

DR. MARKMAN: I won't name names --

(Laughter.)

DR. MARKMAN: -- but that guy figured it out.

So I was incredibly relieved when I saw this patient, and I realized that he wasn't on opioids

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when I saw him, so I did not have to taper him off. But this is a couple times a week, some version of this song. And it's not always this dramatic, but it's a reality. And I think that for these patients who are on high-dose opioids, I think, again, this is part of the complexity of what we face.

I think that we can't exclude these patients like I see a lot of these trials doing. We've got to include these patients or at least we have to have a carve out of a way to study them as well. Because, frankly, I think that there are very few patients in my community who are still on high-dose opioids. A large family practice near me with 24,000 patients, there's only 106 patients on 180 milligrams of morphine a day or greater. I mean, there's just no one out there.

So there aren't that many of these super high-dose patients. Even in 2011 in the VA, only 4.5 percent of patients are on those super high doses. So there aren't that many, in fact, in 2018 I think. So the question is what are we going to

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focus on? And I think this is one area I think that could be relevant.

The central question for me and for all of us, I think, is are patient improvements and group differences to be considered differently in patients with acute and chronic pain and features of opioid-use disorder, as compared to patients with acute and chronic pain in the absence of opioid-use disorder? And I think that's one thing that we have to sort out.

A caveat is most of the studies I talked to today examine voluntary participation in a clinical program or research intervention. The findings may therefore not be generalizable to patients for whom LTOT is reduced or discontinued involuntarily. And again, most patients I think in my life, and probably in other clinicians here, what they're told is -- just like he said -- know, "New York state won't let my primary care doctor do it anymore," or "His university won't let him do it anymore." "His practice administrator won't let him do it anymore." "It's sort of like the hand of

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God comes in and takes my opioids away." Nobody really wants to own that they don't feel comfortable prescribing for these folks anymore.

So I think we have to think about ways of recruiting and enrolling and designing interventions for a world where there's going to be participants who don't want to participate in that activity, for whatever reason. Some of it -- well, you all understand those issues.

So the consensus on what constitutes meaningful dose reduction is needed. Every study says that. You've heard that over and over again today, including patients transitioning to buprenorphine. And again, there's insufficient evidence, I think, with regard to adverse event reporting, and that's really going to be critical because I do think there are as many -- and I thought this was one of the really wonderful parts about Dr. Strain's talk is talking about -- changing things too rapidly I think has been one of the most catastrophic consequences here, saying we're going to just do an about face

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on what we've been doing for a very long time; we're going to go the other way. I think that there's been enormous unintended consequences of that.

So I think that if we institute strategies for opioid sparing, we really got to think about how we're going to get the signal from outside where you're doing that, because clearly, developing abuse-deterrent opioids and doing other things have had other consequences more broadly for society.

A few take-home points for the IMMPACT guidance. There's obviously a need for consensus reporting regarding the appropriate opioid dose, or the range of doses, or what to consider when defining that dose. Obviously, that reduction is going to be different for the patient improvements, where it's probably larger than the group differences, where it's probably smaller.

There's a need to specify treatment in study populations for whom dose reduction is not appropriate, I think a reasonable goal of therapy.

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And there's a need for consensus guidance on, again, reporting these adverse events, whether it's in PDMPs, or state police departments, or whatever social institution we need to harness, or Bluelight, however we're going to surf the internet. But the reality is we need other tools to pick up on the signals that we're creating when we institute opioid sparing on a more broad say.

I'm going to stop there, and thanks so much.

(Applause.)

DR. RATHMELL: Fantastic.

DR. MARKMAN: Thank you.

Group Discussion

DR. RATHMELL: All right. If everybody would come up to the front here, all the afternoon -- nope, all the afternoon speakers. You can come, too, if you'd like.

(Laughter.)

DR. RATHMELL: Some fantastic presentations. I don't know whether to be more dejected or more encouraged. So let's start with some questions, please. And remember, introduce yourself and tell

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us where you're from first.

Rob?

DR. EDWARDS: It's Brigham and Women's. Thanks very much to the speakers. Those were fantastic presentations. I think I have to rhetorical questions for John Markman. I will try and make them brief, and as a rhetorical you won't be obligated to answer.

So rhetorical question number 1. Given your suggestion that opioid-sparing studies and treatments make the most sense, or perhaps only makes sense, when risks outweigh benefits, which I think is a terrific framing, should this group be recommending, when it comes time to make recommendations, that opioid-sparing studies be performed primarily or exclusively in high-risk populations?

We essentially know what those high-risk populations are. Those are folks with a past history of substance Abuse, psychiatric disorders, high levels of psychological distress, and negative affect. I suspect that will be an interesting

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discussion point.

Rhetorical question number 1, given that there's no consensus at all on clinically meaningful dose reductions, should we take a page out of the past clinical trials playbook, borrow a move I think from IMMPACT and ACTTION's past initiatives, and recommend something like a John Farrar style analysis of opioid-dose reductions, where we define some functional or patient-reported global outcomes and tie amounts of dose reduction, either in absolute terms or in percentage terms, to those functional and patient-reported global outcomes, and then hopefully come to some sort of consensus around a number or a range of numbers whereby that could serve as a generally agreed on benchmark for what constitutes a clinically meaningful dose reduction? And it wouldn't be perfect, but it would probably be a lot better than what we've got now.

Thanks. That was longer than I meant it to be.CO2

DR. RATHMELL: So I don't think they're

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rhetorical. G ahead.

(Laughter.)

DR. MARKMAN: The first one, I think I'll leave to others. I think that Brett and I had a conversation about this earlier, about whether everyone is not a candidate for opioid sparing. And he was adamant, I think, that there's a lot of toxicities of opioids that we're not really picking up on and not paying attention to. And if we just think about this too narrowly, we're losing the opportunity to avail patients of many non-pharmacologic strategies to control their pain.

I think his underlying point was that we're too medication focused and centric and too opioid centric. I think that was his argument, or at least his point, that he was making a breakfast. I don't know, Howard, if I got it right or -- I think that was his point.

So I'll stop there. I'll let others -- why don't we break them into two? Is that okay with you?

DR. RATHMELL: Yeah. So stop there, but go

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on with the outcomes and whether or not this -- you kind of glanced over the idea of a composite outcome; a number of the speakers have. And what I think Rob's asked is can we combine some predetermined endpoints for functional improvements and get away from the idea of just opioid-dose reduction alone?

DR. MARKMAN: Yeah. I've always been attracted to the idea -- first, I think this is the question that's being asked about composites. I think that's how we practice clinically. I think that's what we're asked being asked to do when we say that the risks outweigh the benefits; we're saying that the analgesic benefit is a 30 percent reduction in pain intensity and there are no major dose-limiting toxicities, which are causing me not to prescribe. And I think that's what we're often being asked to do.

So I think, composites, I know that a Nat and Lee and I worked on a composite years ago for OMERECT, based on the Cox-2 data that looked at reduction in pain intensity, no deterioration in

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function using the Roland Morris, I believe, and a certain threshold on the Patient Global Impression of Change, and sort of put those three components together as a way of trying to capture, in a more holistic way, an endpoint that didn't just look at pain intensity reduction, or didn't just look at function, or just didn't look at satisfaction.

DR. RATHMELL: Rob, did we get at the crux of your question.

DR. EDWARDS: You did great. Thank you.

DR. RATHMELL: Okay.

DR. MARKMAN: Can I just say one last thing, though?

DR. RATHMELL: Sure. I don't think it will be the last thing.

(Laughter.)

DR. MARKMAN: I agree. When I was on the plane this morning, I was thinking about, I really decided I was going to do an about face. I really didn't want to have to specify a milligram amount and say, well, this number of milligrams is the magic number. And I was really trying to avoid

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doing that. But I think as Rob was asking and challenging us to do, I do think specifying, and stepping up, and giving as clear and as even as quantitative a number as we can is incredibly helpful.

I think one could argue that there's been nothing more catalytic, in terms of having folks interested in drug development in this area, interested in developing therapies and for our own questions, than knowing that a 30 percent reduction in pain intensity is clinically meaningful. I think that's had an enormous clarifying and accelerating effect on so many different research efforts all the way across the entire space.

So I do think the more clarity we give, even if it's not a particular milligram, but anything as close to that as we can get, will accelerate things.

DR. RATHMELL: Please, in the back.

DR. SIMON: Simon, Boston. I'd just like to inform this discussion a little bit about a caveat that we discovered in some of the work that we were

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doing about drug safety, which has a significant impact on our ability to ascertain and measure these side effects that may be associated and a change in the side effects as being an outcome.

We did patient fora to determine whether or not they actually report side effects in clinical trials and in clinical practice. And we actually had the oncology people come to this meeting, who actually informed us about a randomized-controlled trial where they actually used a patient-reported outcome side effects measurement system versus a clinician-ascertained side effect measurement system. And 20 to 30 percent of the patients would not tell their clinician about side effects, either in the RCT or in the clinical practice. And the reason they didn't want to tell was because they were fearful of losing access to the therapy.

In the contextual discussion that John just led, it is really critical. If we're going to think that sparing is measured by a safety series of issues as it relates to the experience that the patient has, what is the context of how they're

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fearful about losing their pain medication, or losing their euphoria, or whatever it is that they are gaining from being on this medication?

We were shocked at the results, and we were shocked what patients were telling us in our patient fora. We actually had over 40 patients that were international, that consistently told us the same thing.

So it raises some questions about what we're thinking about measuring in the context of opioid sparing, and it really raises not just questions in milligram amounts, but it also raises questions about contextually the side effects and if you decrease the side effects. If you can't measure them in any other way besides asking the patient, will we really have data that we can actually use?

DR. RATHMELL: And it depends on who asks them, is a big part of it.

Any comments? Srini?

DR. RAJA: I think that's a very important point, and that relates to some of the scales that have been used to, such as the self-report MADS

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scale versus the MADDERS. In that, one of the issues is in the self-report scale, when there was some anonymity, there's some suggestion of some patient honesty in what they're reporting as long as they feel that there are no direct consequences of that. Bit other scales may not have the same implication.

So I think if you want to get the actual numbers of potential opioid-use disorders, a certain degree of anonymity may be important, I think.

DR. RATHMELL: Please?

DR. STEINER: Hi. It's Deb Steiner again. I have three things I wanted to just ask and clarify. One is talking about composite endpoints. And John Farrar, you can definitely correct me. But my understanding is that a composite endpoint is when you have to hit each of the predefined criteria, and a multicomponent endpoint is when you can hit one of the criteria.

The reason I'm asking is not to be difficult. It's because I think there's a really

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important difference in, first of all, the idea of pain intensity, side effects, whether it's to hit one or both; and then the other is if the discussion's about side effects, nausea, vomiting, then the distinction is would it be acceptable to potentially hit only one of those?

So if I'm off base, pleases somebody correct me.

DR. RATHMELL: Who wants to take on composite versus the multicomponent where you can pass or fail on any one of a number of different predetermined components?

Nat, do you want to take that on? I think that would be reasonable.

DR. KATZ: I actually haven't heard that specific terminology before, but certainly there are differences --

DR. STEINER: You haven't been at Biogen.

DR. KATZ: -- I have actually been there a few times. But certainly there are different ways of constructing composite space on how people perform on the different components. It could be

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an "and" or it could be an "or" which I think is what you were saying.

DR. STEINER: So the terminology forget; just the distinction I think is what's important for the discussion tomorrow.

Then another point I just want to make coming from clinical development is I am all for rigorous trials and everything; I mean, definitely. But trying to propose a trial of 6 months, 12 months duration, like was proposed a little bit earlier today, I think that's going to get -- it would just be difficult for sponsors to do that or for developers to get support for that. So that's just a point to keep in mind, not that I don't support it, just the realities of that aspect of it.

Then my last point was, a little bit earlier today, it was a point made about opioid taper. And I think, Nat, that was in your discussion of study designs. And I just wanted to mention I was actually shocked -- and not in a bad way -- at AAN this past April. There was so much discussion

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about how -- and by people who treat pain, by people who are knowledgeable, how they're managing their patients, and experts asking other experts. So I just think that's a really important aspect, especially coming from the sponsor's side because the sponsors need guidance on that. That's all.

DR. RATHMELL: On opioid taper?

Do you want to add something, John?

DR. MARKMAN: Your last question, your point about limiting to shorter duration studies, you mentioned the AAN. When I look at the duration of studies in other fields, 6 months, 9 months, 4 years, 5 years, recent Alzheimer's trials, these are multiyear studies.

Why is it not feasible to do a 6-month study or a 9-month study in our field? Obviously, these companies are clearly willing to undertake these. And partly because I think there's so much societal pressure to have more long-term evidence for analgesics. I mean, that's I think at the root of a lot of the narratives.

DR. STEINER: I think that there are two

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reasons. There are other reasons. One reason is I think that people who work in pain are aware of the number of negative trials, and failed trials, and just the concern that the longer you go, is it just a waste, and should you do an interim analysis, and you have to make a bigger trial to save your alpha, and that type of a discussion.

So I think that's a biggie. And the other is just, realistically -- and I don't know if that would be true in this type of study design, but they're just high dropout rates. I just think from the sponsor side, those are concerns.

DR. STACEY: Brett Stacey. I want to say one more thing about that, too, which is, we give people long-term opioids expecting them to potentially be on them for the rest of her life, yet we have studies that are 12 weeks in duration upon which we base that. In the endocrinopathy, the depression effects, those are later effects that are not going to show up in those studies, and the difficulty with tapering, and the micro withdrawal.

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All those things have been discussed -- a lot of those things that have been discussed are long-term effects. And the reality is that it's difficult to have long-term studies. It doesn't mean that they're not needed and we shouldn't support them.

DR. RATHMELL: Please?

MS. COWAN: I think the thing you have to remember is you're tapering them off. They still have pain, so you're going to have to do something else for them. And I think that's a missing piece, that we're trying to taper them off opioids but what else are we doing to help them manage that pain? I mean, there are a lot of things, and I've said this before. But keep in mind as you taper them off, it doesn't mean their pain's going away. So what is -- I don't know.

DR. RATHMELL: I think a number of us should respond to that. This is an everyday discussion that we have in the pain clinic that just says, but what about my pain? And the hard part is, after doing this for many, many years, you can taper in

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such a way that the report of the pain intensity doesn't change over time, you haven't abandoned the patients, and yet you really haven't added anything back into the mix that's really added meaningful new analgesia. That's a really difficult conversation, and it means a lot of trust over a long -- you can't do this the first time you meet somebody in the clinic.

Do other people want to respond to that? Because I hear exactly what you're saying, and it's a conversation we have all the time.

MS. COWAN: One of the things we always say is for people when they are told, "learn to live with it," that's not something any of us know how to do. It's not an instinct that we have. We have to teach them how to do that. And that's always been the missing link, is teaching them. And you can, but you've got to support them, which means providers, a whole group -- I mean, it takes that team. Someone had a team slide up there. But it does take a whole team, and that becomes expensive, so that's another whole issue.

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DR. RATHMELL: Anybody else on pane? The panelists are remarkably silent on this one, despite probably everybody having been in these shoes.

DR. FARRAR: At the risk of interrupting, which I'm going to do anyway --

(Laughter.)

DR. FARRAR: -- it won't surprise folks.

DR. RATHMELL: Who is that interrupting? I don't know.

DR. FARRAR: John Farrar, a very quick comment. You asked about dementia trials and seizure trials. It's because seizures are easily to diagnose and dementia is something that is measurable over time with certain scales and other things that people have much more confidence in.

You know and I know that I've got a patient who says every day, their pain is a 7 out of 10 and sometimes it's a 9 out of 10. You give them medication; it goes to a 7, and they come in, "Today my pain is a 10." We don't have scales that are appropriate for long-term studies because the

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zero to 10 scale is clearly not appropriate for a 6-month or 12-month study. I had one patient I measured his pain in baskets. If he brought me a basket, it meant he was feeling better because he had the time to weave it. If he didn't bring me a basket, I knew he was in trouble.

I don't know how to deal with that over the long term. I think one of the problems in the longer-term planning is how do you deal with that. The second is that as soon as people stop whatever medication that is being used, as Penny was just saying, other things get done, and the drug company is not interested in what happens to them after that.

DR. RATHMELL: Let's move on to some other areas.

Rick, do you want to --

DR. RAUCK: Richard Rauck, Wake Forest. This is for Raj. Thanks, all you guys, for a great talk. In listening to everything today -- and since I have to do some of the moderating tomorrow for the acute pain stuff -- when I listened to all

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of those studies you showed on the epidemiology, and I think back to even Eric's comment, which I wrote down so I would get it right, which was just getting opioids to people is not the reason people misuse them.

If I had to take away a message -- and I think it's relevant to why we think opioid sparing may be effective in acute versus chronic pain, and I'm more of a chronic pain guy than acute pain -- it sure looked to me like those epidemiology studies suggest and support that there isn't really increase abuse from just the exposure in the acute setting. Those were so small numbers, you could almost say that's less than what we would think of as the incidence of abuse just by general population parameters, 0.6 percent or 1 percent of Brett's work. I could even say that 4.1 percent versus 1.3 percent is 3 times higher, but maybe those people got opioids because they had a worse problem at the time of discharge. That relationship is not a cause and effect necessarily for why they're getting opioids.

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So I think it would be relevant if we all agree, or if you agree, or how we have that discussion, then we could move away from that we're going to do opioid-sparing trials in the acute pain for reasons other than just abuse, taking away a little bit I think Brett's point about more pills available. Let's leave that aside and the reason we might want to send them out with less pills.

Do you think that's a fair conclusion, Raj, or would you draw something different out of all I've heard today?

DR. RAJA: I think that's fair, but with some caveats. When I was looking at the first study which I presented on the Denver population in terms of patient hospitalization for acute pain in opioid-naive patients, I was impressed by the fact that a year later, the proportion of patients getting prescriptions in patients who were admitted for non-surgical indications were considerably higher, twofold higher than the patients going for surgery. You would think surgery would be clearly causing pain, but a number of those patients were

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admitted for non-surgical indications. Few of them were pain, chronic pain, but the majority of them are not chronic pain patients.

So here is a population that were opioid naive to start with, had some kind of an acute episode that required hospitalization, and they were sent home with a prescription. And then 12 months later, they seemed to have a higher proportion or higher risk for being maintained on opioids.

So I think there's something inherent about being sent home with an opioid and continued with that, but what is that risk, and who are those populations at risk is important. This comes along, back to the questions that Bob initially posed, as should we have a composite measure or develop a meaningful dose reduction type of measure?

I think that makes sense, but what we need is to define a clear dose-response relationship across different adverse effects. For example, respiratory depression clearly is dose related. At

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least in chronic pain patients, constipation doesn't seem to be dose related. Even with the first dose, they may appear to be constipated. And even in those large epidemiological studies, the risk of opioid-use disorder, there wasn't a clear dose-response relationship.

So I think what we need to develop first is look at outcome measures, look at the different adverse effects, develop in which of these doses adverse effects are clearly dose related. And there, maybe you might shift the needle somewhat. But that requires more granular data on the different adverse effects and the relationship of those adverse effects to dose.

DR. SANDBRINI: Friedhelm Sandbrink. I'm from the Washington D.C. VA medical center. I want to talk a little bit more, actually, about the effect of the dosage. By looking at our VA data, our patients on opioid medications in the past, who are taken off opioid medication; that's one data source that we have. And then, in particular, we have been starting to analyze all our patients who

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had a history of opiate exposure and then had an overdose or suicide in the recent years.

What we find is that the majority of patients that die of an overdose of opioids are not on high dosage. Yes, individually speaking -- and I think that's what the graph showed of the Bonid [ph] study that we saw. Individually speaking, the risk is significantly elevated if you are at high dosage, but the majority of patients who actually die, 80 percent in the VA system are below 100 milligrams of morphine equivalent. The majority are 20 to 50 milligrams of morphine equivalent.

When we look at the data of what drives the risk of an individual patient, the greatest risk comes from mental health comorbidities. That drives the risk. Any past admission to an inpatient mental health service or psychiatry service drives the rest 20 times; that's any past history, whereas in our study, the benzodiazepines drove it only by a factor of 1.4.

So I think if you're talking about opioid

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sparing, we have to really study -- we're trying to shift from less risk to more benefit. And why are we making that equation? Which are the patients at risk?

Now, the factor of co-prescribing sedative medication is another huge factor that we see in our data, and that includes what we consider evidence-based therapies for pain, such as the anticonvulsants that are sedating, muscle relaxant, maybe antidepressants that are sedating. These factors are quite relevant in itself and have independent risk factors.

So when you're talking about, then, which patients would be tapered, I'm very concerned about them taking these highest risk patients to actually taper them because many of them really need to not be tapered, but need to be switched over to opioid-use disorder treatment with MAT [ph], because if you taper those, those are at risk for opioids, but they are probably at an even higher risk when do you taper them inappropriately fast.

That brings me to my last point -- and I

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very much appreciate you showing Beth Darnall's study and the Stanford group about the patient-centered tapering, is that we feel we need to know what the patients actually want to do. If you do a study and you're doing something about opioid-dose reduction, you need to know where is the patient? Is this patient motivated to come off opioids? Is this patient confident that if you do an opioid-dose reduction that they will be successful in managing their pain?

So these are factors you need to analyze and need to know from the patient as you make your treatment decisions, or as you your studies and try to see what's going to be my outcome. So I think you need to have information about where the patients are in this continuum of care, and you need to be very individualized as a clinical recommendation what you do with that.

DR. RATHMELL: Ian?

DR. GILRON: Sure, thanks. Ian Gilron from Queen's University in Canada, where the opioid crisis is also alive and well. Thank you,

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everybody, for excellent talks. I think we're supposed to make recommendations about clinical trials in acute chronic pain, so my one question is, should we be recommending any clinical trials where opioid consumption is the primary outcome? And if there are any situations like that, what would that look like?

DR. RATHMELL: Shannon, do you want to take a stab at that?

DR. SMITH: To me, I think that missed the whole picture. I think if we just look at opioid dosage, it doesn't include things like pain or functional outcomes. So it's hard for me to see that as being a valuable endpoint in and of itself.

I don't know. Do you have thoughts on whether or not that's valuable, Ian?

DR. GILRON: Well, since you said that, should we say that we do not recommend opioid consumption being a primary outcome? I suppose a co-primary could be something we could consider, but, yeah. It wasn't a trick question. I just want to know how we're going to articulate that in

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the recommendations.

DR. RATHMELL: I chose Shannon because she went through all the literature that shows we focused on opioid consumption, and we really don't know that there's any clinically meaningful outcome associated with -- that's the crux of the matter.

DR. GILRON: And to be fair, because, yeah, you didn't really comment on some of the quality of some of the studies. Sometimes we know from other ACTTION-IMMPACT studies, there's some harkening and some mischief going on, and sometimes it's the only positive p-value that comes out, and it ends up getting articulated as a primary outcome. So certainly, we're not racing to that bottom. The question is, should we say a little more forcefully that we don't recommend a sole primary outcome?

DR. RATHMELL: That's probably one we should park. It's on the record, right? Is reduction in opioid dose alone, as a primary outcome measure, either acute or chronic, viable in studies going forward? And we ought to come back to that tomorrow.

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Bob, is that a reasonable thing to try and come back to as we conclude tomorrow?

DR. MARKMAN: I just would give you my own two cents. I think it's all contextual. For me, there's a legacy population of patients who are still marooned on high-dose opioids. They're not that many, but they're still out there; they're here and there; or people who get stuck after surgery and can't come back down. Mostly I think in that population, they're extremely motivated to come off but they're definitely afraid of re-experiencing opioid withdrawal, and they often confound their opioid withdrawal with either a worsening of the underlying pain problem or something else.

I do think in that population of patients, that's where buprenorphine is uniquely valuable and another drug like buprenorphine that also functions in that way. It's just a tool to get patients through that moment of utter fear of withdrawal. And once they go to the other side, there are so many patients who do feel better. They just don't

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want to go back into withdrawal. Just like someone who has a primary substance abuse problem, a lot of what they're doing is trying to attenuate the intensity of that withdrawal episode.

DR. GILRON: But if you did a trial of buprenorphine for transition, what would the primary outcome be? By design, your pre-buprenorphine opioid would go down to zero.

DR. MARKMAN: So you're saying it may be a binary thing where you're on or off.

DR. GILRON: I can't see that being a primary outcome because if you're doing a study of buprenorphine, like transition to buprenorphine, they would just come off their previous opioid.

DR. MARKMAN: And then they taper off buprenorphine. I mean, that's typically what happens is -- it's been my experience that almost 40 percent of our patients who transitioned to buprenorphine, because of the kinetics of buprenorphine, just like we talked about PK before, can gradually step down their buprenorphine in a way, which is much more feasible than trying to

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come off a premier [ph] opioid agonist.

DR. GILRON: So I guess the question is, if we did a trial like that, I guess what would the design be and what would the primary outcome be?

DR. MARKMAN: Again, I think you could look at either abstinence at a certain time point, or being off opioids and compare that with pain, looking at pain intensity as a secondary, potentially.

DR. SMITH: Does buprenorphine have a morphine equivalence? So could you use that? I don't know.

DR. MARKMAN: Some of us, there are rules of thumb that folks use, depending on the primary indication. But yes, certainly an oxycodone equivalence that folks use the community.

DR. SMITH: So then you could use opioid sparing as one of the outcomes if you were doing a switch to buprenorphine study --

DR. MARKMAN: Based on that conversion.

DR. SMITH: Yeah. That's what I'm saying, yeah.

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DR. MARKMAN: And that's been done, I think. I think Nat's been involved a little bit with that, too, with Belbuca, right? I think there was some of that around Belbuca. I think there was some of that around Belbuca and the development of that program, because obviously in that clinical context, you had to transition patients who were on another opioid to buckle buprenorphine. Dr. Rauck and also others were involved in this. And I think there was a lot of analysis about that transition from another morphine equivalent to buprenorphine in that study.

DR. RATHMELL: Srini, do you want one more comment? And then we'll go on to --

DR. RAJA: Yeah. I just want to make a common -- or a question for discussion because there are a lot of acute pain, perioperative pain experts here. If you're looking at the issue of opioid-use disorder in patients given prescriptions after surgery, would the duration of these prescriptions be a factor that we should be looking at in the design of the study? And if so, what

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should be -- there seems to be at least suggestions from the epidemiological literature that how long these patients get after surgery makes an important difference.

So should this be an outcome measure that should be studied in acute perioperative studies? It's just a question for some of the experts, maybe for you as well as well, Brett, and some of the experts that are here.

DR. RATHMELL: I want to give Michael a chance.

DR. OSHINSKY: Thanks. I just wanted to go back to a previous comment that was made, that sponsors are interested in funding studies that are more than a year long.

This is Michael Oshinsky from NIH, specifically from NINDS, which is the National Institute of Neurological Disorders and Stroke. Our typical grants that we give out are 5-year grants, which definitely allows for tracking the patient for more than a year. And from my perspective of looking at literally every single

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pain grant that comes into NINDS for the last 4 years, there's a dearth of applications, that are specifically clinical trials, that are addressing fundamental questions to change clinical practice.

The vast majority of them that come in are, does this work or does it not work with novel treatments or even -- to be honest with you, not novel treatments. And those do not do well in review. But really fundamental, strong, scientific questions that require long-term follow-up with the patients, et cetera, we know that's what NIH is designed for, those types of trials. We know that private sponsors don't sponsor those.

So those fundamental scientific questions are the type of the ones that do well in review. So this is just a public service announcement.

(Laughter.)

DR. OSHINSKY: No, no, no. You'll see what I'm saying. If you have an idea, a scientific idea, do not dismiss as being not something NIH is interested in without contacting somebody from the program staff. It's just so many times I've heard

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people say I had this idea 10 years ago to do X, but I didn't think NIH would ever be interested in it. And they're really good scientific questions.

So please reach out to the program staff and vet your ideas, because we have lots of different mechanisms to support the fundamental questions that you guys are bringing up at this meeting.

DR. RATHMELL: And now a question from one of our short-term sponsors.

(Laughter.)

DR. STEINER: I'll be really quick again. Deb Steiner again. I just wanted to mention that when I first brought up this meeting to Biogen group, and I was all excited, and I'm like this sounds great, I kind of just got these blank stares, like what are we going to do with this?

So not that I'm endorsing looking literally at opioid use as a measure, but just from the vantage point of if one of the outcomes of this meeting is to be able to come up with things, which not only will be utilized by sponsors but would partly be, I'm thinking about how are some of these

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measures going to be used because the thought is, what are we going to get on the label; how are we going to get payer reimbursement? So that's all. Thank you.

DR. RATHMELL: So get real esoteric and don't get too esoteric. I got it, but be practical.

TJ?

DR. GAN: This is just a question to Denham. I think you are the only one that hasn't spoken on this panel yet, but can I ask you a question? TJ Gan from Stony Brook.

You had showed the combination of opioids and promethazine, and that promethazine does not increase a risk of opioid suppression or breathing. And at the same time, you showed it's quite different between promethazine and prochlorperazine. Why is that such a big difference given that both has MT [ph] dopaminergic? That is one question. The second is, once you add benzodiazepines, that risk of respiratory depression goes up substantially on

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both sedatives.

Can you address those two questions?

DR. WARD: It really wasn't -- and I was probably a little confusing in my talk. But as far as the centrally acting chlorpromazine, phenergan, any of that group, they do very little to potentiate the hypercapnic depression of the opioids. But they both are dopaminergic antagonists, D2 receptors, and the carotid body has D2 receptors. And blocking a D2 receptor in a carotid body increases the hypoxic response. The dopaminergic receptor and the carotid body inhibits the hypoxic response.

So for one of them, I didn't give you -- they didn't measure the hypoxic response. They just showed there was no difference in the hypercapnic response. The other study measured both the hypercapnic and didn't find any difference. Also, the hypoxic response showed an increase, a stimulatory effect.

Droperidol does the same thing. Droperidol increases the hypoxic response, and therein lies

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the difference between those and the benzos, although obviously completely different receptors, but the GABA receptor is always an inhibitory receptor. So the benzodiapzepines at the GABA receptor are going to cause central depression, and probably be removing the wakefulness drive more than an actual effect on the chemosensitive drive themselves. Benzos by themselves almost have no respiratory effect. Benzos plus opioids have a large respiratory effect, again, probably because of removing the wakefulness drive.

So really combining two things, you've lost the metabolic hypercapnic chemoreceptor drive because of the opioid, and you've lost the wakefulness drive because of the benzo, and you're not left with much drive, so you get pronounced respiratory depression.

DR. RAJA: So sedation really is not the problem. It's the other aspect. We comment and say it's because of sedation, which is really not quite --

DR. WARD: Right.

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DR. RAJA: -- accurate.

DR. WARD: That would be correct.

DR. RATHMELL: Ajay, and then Jennifer.

DR. WASAN: Hi. I'm Ajay Wasan from the University of Pittsburgh. I have two quick comments that maybe the panel can react to, and then Dr. Fields had a comment, and then Dr. Haythornthwaite had comments as well.

First of all, I think a lot of the tone that we've heard so far has been, I wouldn't say negative, but this idea that we don't have good enough data to make good enough research recommendations in a paper. But it seems to me that we actually have a lot of reason for positivity here because we're hearing about a lot of possible outcome measures, which seem relevant, and a lot of possible designs to get at those questions, too. So I think that would be important to emphasize going forward.

The second thing is, one thing we haven't brought up or talked about that I think is relevant is this idea of whether there are proxy measures of

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opioid sparing that we should consider. So for instance, if you do a study that would decrease a risk factor for prolonged opioid use -- so it could be neuropathic pain symptoms; it could be sleep symptoms; it could be psychological symptoms -- would that be considered in this vein of opioid sparing, meaning to be a valid and reasonable opioid-sparing design? So something to think about.

DR. RATHMELL: Howard, would you say your name?

DR. FIELDS: Howard Fields, University of California, San Francisco. Just a general comment, there's a lot of variability from patient to patient in the dose that would be required for them to have an analgesic effect. These adverse effects also have a dose-response relationship. We saw that. I think John's comparison of fentanyl with buprenorphine was a great example. That's going to be different for each side effect.

So maybe a way to think about this is instead of opioid sparing, maybe it would be better

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to talk about dose optimization and think about a thing called a therapeutic window, which you want to optimize. So the thrust being, what we want to do is we want to better manage pain.

So the Stanford study, one of the reasons that I thought it was so cool was that they were actually able to show that some people did at least as well with a much lower dose of an opioid, which meant that the dose they were taking was higher than they needed. They called it a taper, but they were optimizing the dose. So it might help us around a lot of these semantic puzzles that Nat brought up earlier in the day, don't call it opioid sparing because that's going to mean different things to different people. Call it dose optimization, then the ideas is it's patient centered, and it's what we're interested, the best pain control with the lowest number of side effects.

DR. RATHMELL: Or the lowest effective dose.

DR. FIELDS: Or lowest effective dose, which is the best way to use them.

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DR. RATHMELL: Jennifer?
DR. HAYTHORNTHWAITE: So that actually crosses over with the point I was going to make. And I just keep hearing there's so many important subgroups. Sorry. This is Jennifer Haythornthwaite from Johns Hopkins.
DR. RATHMELL: I was going to add that at the end.
(Laughter.)
DR. HAYTHORNTHWAITE: Thank you.
DR. RATHMELL: I'm tired of doing it at the beginning.
(Laughter.)
DR. HAYTHORNTHWAITE: There are so many different subgroups that we're talking about, so the VA, if they have a mental health disorder, or if there's a kind of a co-occurring medicine like a sedative. It seems to me that we want to not only think about acute versus chronic pain, but we want to think about the clinical context of the patient.
So off treatment optimization also brings in, what if you have patients that are high risk

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for opioid-use disorder? Treatment optimization is not just about pain and side effects; it's long-term opioid risk, so that we really start to think not as just these two acute versus chronic subgroups or clinical context, but we think of within each of those, there are other important subgroups that we start identifying from the get-go in terms of in need of possibly more research, but definitely I think there are clearly subgroups that could go into clinical trials.
The issue with the Darnall study that's really important, and we find this with behavioral studies all the time, we don't know who steps up to the plate in volunteers. We can't characterize them. We just know who comes, and we know that they're willing to do the study. But we don't have really good characterizations of their motivations. And you know that there are lots of reasons why people don't show up for the taper study as well as the behavioral study, but we don't have a way of -- and we need to start operationalizing those really important characteristics of the subgroups

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that we know are part of the patients.
DR. RATHMELL: Imagine an acute pain study, even a simple acute pain study where you took all-comers, and you actually characterized those who enrolled, those who didn't enroll, and what the reasons for that were, and then follow them longitudinally. That's just not something that we've done to date. Right? It's difficult.
DR. HAYTHORNTHWAITE: Yeah. And when you get to chronic pain, it's even harder. So let's say you have somebody in care with a provider like John who's willing to hold their opioid dose stable. Well, how motivated are they, given that relationship and the conversation they've had, to sign up for a tapering study?
So if you're just interested in opioid sparing, you're not going to engage people in the same way. So the whole idea of maximizing dosing might be a perfect way around --
MALE VOICE: Optimizing.
DR. HAYTHORNTHWAITE: -- sorry, optimizing, not maximizing.

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(Laughter.)
DR. RATHMELL: I think you said minimizing dose.
DR. HAYTHORNTHWAITE: Big mistake.
DR. RATHMELL: Lowest effective dose.
Michael? Who are you?
DR. ROWBOTHAM: Michael Rowbotham, Sutter Health and UCSF. Just one comment since there are so many clinicians on the panel right now, that John brought up about the fear of pushing the button on Epic screen. Physicians are all being tracked as to how much opioid they're prescribing. And absolutely, you're being tracked by whatever healthcare system you're working in. You're being tracked on various state and national pharmacy databases. And the reason why academic pain clinics see such a high proportion of what you call opioid refugees, which is a good term, is that you're the only ones that can get away with prescribing without sanctioned scrutiny and unpleasant interactions with your chief medical exec, wherever your physician practice is.

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So it's a real issue, this stigmatization. And I've had health insurance companies come to me and literally, they will have the charts on all the patients who are, let's say, over 300 morphine equivalents per day. They know all of them and are tracking how they're being managed.

So even though we may discount that as an outcome measure, that's what the insurers and the healthcare systems are often looking at. They don't care about anything else except number of prescriptions and MEQs.

DR. RATHMELL: Yeah, but honestly, from our own local experience, we see in our own ranks huge disparities amongst the chronic pain physicians. So what else would you do as an insurer when you say you all have the same subspecialty designation, and yet we've got this same -- "What the heck is going on here? You're seeing the same group of patients, aren't you?" That's what they're saying to us.

So we need to have some common philosophy, and that's my feeling, at least within a single

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clinic because, otherwise, the patient who comes on Monday, they get one treatment. They come on Friday; they got a completely different treatment, in the same clinic and the same health care, and it drives practitioners crazy, and patients, obviously.

Please?

DR. JAMISON: John, a good part of your -- oh, I'm sorry.

DR. RATHMELL: No, that's good. I'm going to keep going.

DR. JAMISON: Bob Jamison Brigham and Women's Hospital, Boston. I think I can't wait to read this paper when it comes out.

(Laughter.)

DR. JAMISON: The memorable part of your talk, John, is the individual differences, and it reminds us, every once in a while, we're dealing with a lot of different people, and how do you track that? So how do you come up with guidelines that are going to be for everybody, recognizing there are huge individual differences?

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Something that may come up tomorrow -- I appreciate any of your thoughts on this today, but how do we use innovative technology to track people better than what we have right now to help us understand how people are using opioids, and then how does that help make decision-making? So we're talking about activity monitors, we're talking apps, we're talking about a lot of the things that are out there now that are futuristic, but they're available.

So I'd be curious of anybody's reaction to that in terms of how we really understand individual differences in response to opioid use.

DR. RATHMELL: There's an app for that.

(Laughter.)

DR. RATHMELL: Anybody want to comment on using these?

DR. STACEY: I'll make a quick comment. There is going to be lots of great options I think for that, ranging from the Smart Bottle that opens -- every time it's open, it tracks. Then you have it hooked up with an activity tracker. So the

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patient opens the bottle, takes a pill, then they go sit on the couch; or they open the bottle, take the pill, and then go out and does the yard work. Those are very different outcomes, and you can track that.

There's also some talk for select chronic pain patients and an intensive study that would require deep pockets of basically wiring their home to track each time a door's open, so you can track their movements within their home, when they leave the home, that kind of stuff, to look at their activity levels to associate with it. There are ways of looking at -- even just with a fitness monitor -- there are a whole bunch of things you can do, and I think we really don't explore those things very much.

I'm sitting here listening to this conversation and thinking if I'm in drug development, boy, what drug am I going to come up with that's going to really be the one for chronic pain opioid-dose reduction. I don't think anybody is like really burning with that. It just shows a

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big separation between the acute world and the chronic world. And also, Jennifer's point about the subsets, about the differences, how different the patients are, and we need to really look at these different types of patient populations.

I ask patients really simple questions like, "Do you read?" I don't suggest Beth Darnall's book about tapering opioids if they don't read. So there's like really simple things that kind of separate people out, like what do you do for fun? There are a bunch of things that help separate things out that are not ever going to be in a clinical trial.

DR. RATHMELL: John, you want to comment quickly? And there's one last question.

DR. MARKMAN: I'll be a little bit of a passive monitoring Luddite. I will tell you -- and the reason why I think -- I think that the history and the narrative are the most important part when it comes to pain probably because of what John Farrar said, is because we don't have another tool. To me, all of these reductions, how much you moved,

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or how many times you opened the bottle, I'm just worried that those get over-interpreted in a way, that self-report -- they just don't have the richness of self-report and give you the context.

I always feel -- I think those are great adjuncts to the self-report, but I truly fear the world where we take away someone's opioid because they haven't walked enough. And we don't really understand why they haven't walked. Maybe they also have vertigo. So my concern about all the passive monitoring -- and my own institution is really enamored of this -- is the fact that unless it's coupled with a PRO, I just feel like it's very hard to interpret.

DR. RATHMELL: Last question?

DR. C. BROWN: I had a comment on --

DR. RATHMELL: Sorry. Just say --

DR. C. BROWN: Cole Brown, Innocoll. I had a comment on two statements that were made earlier. One was the question posed around utilizing opioid sparing as a primary outcome. I just wanted to orient regarding the clinical development of an

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acute postoperative analgesic. I think if I'm developing a drug for postoperative pain, I think primarily what I'm going to need to prove is that it does reduce pain intensity.

So the second aspect is important, that opioid sparing is very, very important, so considering it as a co-primary. But as developing an analgesic, I think I need to demonstrate that it decreases pain intensity first and foremost.

Then a second comment was regarding to following opioid sparing for a longer time period. I think that's interesting, and one I guess concern that I would like to pose to the group is, yes, there is a good amount of data showing that if you can decrease the severity of pain intensity in that initial acute postoperative period, that perhaps you are decreasing the pain intensity further down the line. But on let's say day 6 or 7, the assay sensitivity, that delta between the drug I'm developing and placebo is really decreasing, so I'm not really going to be able to show that difference. So we're maybe losing that if we

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follow it for a longer period of time is my only concern.

DR. RATHMELL: And a very reasonable concern. But what if that initial difference between the new drug and conventional analgesics looked at 6 months later and, even though you only use the drug for 7 days, actually changed something about drug use habits 6 months down the road in patients who may have had persistent opioid use? That's the kind of maybe it will, maybe it won't.

Anyway, I want to thank everybody for all their input here. Any words of wisdom from our organizers?

(Applause.)

Adjournment

DR. RATHMELL: So dinner is at 7:00, and it's in the room where we've had all of our meals thus far.

(Whereupon, at 5:32 p.m., the meeting was adjourned.)

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