

*ACTION - IMPACT XXI - OPIOID SPARING IN
PATIENTS WITH ACUTE AND CHRONIC PAIN*

July 26, 2018

*A Matter of Record
(301) 890-4188*

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

July 26, 2018

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6	ASSESSMENT IN CLINICAL TRIALS	
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12	Clinical Trials of Opioid Sparing in	
13	Patients with Acute and Chronic Pain	
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16	Thursday, July 26, 2018	
17	8:15 a.m. to 5:32 p.m.	
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20	The Westin City Center	
21	Washington, DC	
22		

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1 itself. It subsequently was folded into the

2 ACTTION initiative. ACTTION stands for -- and Bob,

3 you'll have to correct me because I always get this

4 mixed up -- stands for Analgesic, Aesthetic,

5 Addiction, Clinical Trials, Translations,

6 Innovations, Opportunities, and Networks.

7 You may be wondering why aren't there three

8 A's there. Historically, it started out with one

9 A; it was just analgesic. And this is a

10 public-private partnership between the University

11 of Rochester and the U.S. Food and Drug

12 Administration. A public-private partnership means

13 we work together, but it should not assume -- no

14 one should assume that anything that we have

15 published or that we've put out is the result of a

16 governmental policy or the FDA policy. It is just

17 the discussions, conversations, agreements that we

18 have among those people in the group, who then will

19 create manuscripts.

20 Of you're familiar at all with IMMPACT,

21 you'll know that there are IMMPACT manuscripts. By

22 the way, ACTTION.org or IMMPACT.org, you can go see

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1 P R O C E E D I N G S

2 (8:15 a.m.)

3 Welcome and Introductions

4 DR. TURK: Good morning. I want to thank

5 you all for being here for this particular meeting.

6 This is the 21st IMMPACT meeting. For those that

7 have been around that long, they've been to some of

8 those. Some of us had black hair when they

9 started; the rest of us look like me.

10 (Laughter.)

11 My name is Dennis Turk. I'm from the

12 University of Washington in Seattle, and I've been

13 involved with Bob Dworkin with the IMMPACT meeting

14 since 2002, I believe, so we've been here for a

15 while. I want to thank the sponsors who are

16 supporting this particular meeting. That includes

17 the public-private partnership from ACTTION, which

18 you'll get used to these acronyms. I'll just tell

19 you what they are, ACTTION and IMMPACT.

20 IMMPACT is the Initiative on Methods,

21 Measurement, and Pain Assessment in Clinical

22 Trials. It originally started out as an entity in

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1 all the background papers and manuscripts that

2 we've developed over time.

3 I don't see Sharon Hertz or Allison, and I

4 can't see all that far back. But those are the

5 people from the FDA who have worked heavily with

6 us, and I want to thank them for all of the

7 assistance they've given us over the years since

8 ACTTION began, which was 2012. So IMMPACT started

9 2002, and then it moved forward.

10 What we're going to try to do today is take

11 up a very interesting issue, task, a timely one,

12 which is related to the concept of opioid sparing

13 and how its relevance and importance are going to

14 be handled within clinical trials of acute pain and

15 chronic pain. So we're going to be a little

16 schizophrenia because we'll be going back and forth

17 between acute and chronic pain.

18 But the goal, however, is to talk about,

19 first of all, what do we mean by opioid sparing.

20 Why is it important in both acute and chronic

21 trials? How do you measure this? Do we consider

22 objective measures, subjective measures, both of

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1 those types of measures? How do we use those?
 2 What's a clinically important or a meaningful
 3 effect of any type of treatment? Is it from the
 4 patient's perspective? Is it from the actual
 5 provider's perspective? Is it from the actual use
 6 of the drug?
 7 The way that we formatted this meeting is to
 8 address those types of topics, and you'll hear much
 9 more detail about those. If you look at the
 10 agenda, you can see all the things that will be
 11 covered. We purposely intentionally structure all
 12 IMMPACT meetings -- and this one in
 13 particular -- that we have lots of breakout time,
 14 coffee breaks, lots of lunch times, dinner times;
 15 the idea being that what happens in this session,
 16 these meetings, that's just part of it, maybe even
 17 the smallest part of what's going to come out of
 18 this, because we're hoping that that leads you to
 19 raise questions, to have more discussions among
 20 yourselves, and to then bring them up to the group.
 21 We've also structured that by the end of the
 22 day tomorrow -- and we won't let you leave until we

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1 do this -- we have to come up with some
 2 recommendations. So if any one of you here was
 3 going to plan a clinical trial next week, you would
 4 have some suggestions, some recommendations, and
 5 some considerations for you. Admittedly, we're all
 6 going to say, you need more data, you need more
 7 evidence, et cetera. And that's true, but if
 8 you're writing your grant on Monday, you can't wait
 9 for all those data. So what you have to do is go
 10 with what's the best information you have at this
 11 particular point in time.
 12 So we will come up with some
 13 recommendations. Everyone in this room is invited
 14 to be an author of those manuscripts. And what
 15 that means is we have a person who is what we call
 16 a rapporteur.
 17 Jen, are you -- where is Jen? I can't see
 18 her. Would you stand up just so people can see
 19 you? She's an important person because Jen is
 20 going to be taking notes and minutes. And if she
 21 hasn't understood something you've said, she's
 22 going to come to you and try to make sure for

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1 clarification, because she's going to make the
 2 first draft.
 3 Now, we totally understand that when we
 4 leave tomorrow, or when you leave tomorrow, that
 5 this isn't a final product; that we still have
 6 issues that haven't been resolved to be discussed.
 7 What Jen will do is draft up a manuscript. The
 8 steering committee will review it and add comments
 9 to it. It will then go to all of you, asking you,
 10 begging you to look at this, to make comments on
 11 that, make suggestions, things we left out, things
 12 that were unclear, things that we didn't define
 13 appropriately.
 14 We'll give you a reasonable time, and by
 15 reasonable -- as you look around the room, you see
 16 the number of people here, and you can understand
 17 what fun that is trying to get 50-plus people to
 18 agree. Now, if you choose not to or if your agency
 19 that you are representing won't permit you, that's
 20 fine. We understand that. But if you do want to,
 21 then we strongly urge you to make sure you follow
 22 the deadlines, and suggestions are going to be

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1 given.
 2 Having done this a while back, let me tell
 3 you that someone sending an email saying, "Great
 4 job" is not real helpful, or "There's some
 5 grammatical errors or typos," that's not helpful.
 6 So what we really need from you is not just those
 7 kind of comments, which are fine if you catch them
 8 because surely there will be some of those. But if
 9 there are certain points that you think we really
 10 need to make, or we missed, or we need
 11 clarification, you think should be expanded, need
 12 to be shortened --
 13 We've initially envisioned this as being a
 14 single manuscript. However, it may be the case
 15 that that's too much to try to cover in one paper,
 16 so it may end up there will a separate one on acute
 17 pain and a separate one on chronic pain because of
 18 some of the uniqueness's of those. We'll see if it
 19 works that way. But those will be circulated. It
 20 takes usually 3, 4, 5, 6 months before you'll see
 21 something, so don't think we've forgotten you.
 22 All of the presentations, all of the

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

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

22 So that's just the logistics about the

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

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

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

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

7 Sign the registration if you haven't signed
 8 in, and that means sign in and out both days so we
 9 know who was here. Cell phones, silence them.

10 You've heard that enough times, if you go into a
 11 movie or a meeting. Please do that. It's really
 12 distracting to presenters. I mentioned about
 13 the -- they're not voice activated, so disregard
 14 the microphones. Go by what I told you. You have
 15 to push the button. They're not voice activated,
 16 too many people. And only a certain number can be
 17 lit up at one time. And if you try to push the
 18 button when there's too many on, you just get a
 19 blinking red light. Just wait for your question.

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

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

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

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

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1 reliability check to see if you've learned
2 anything, where to go. Check out is 12:00
3 tomorrow. There's luggage either at the bell stand
4 or we'll be able to store it for you here.
5 If you need any assistance, as I said, talk
6 to Valorie or Julie, and they're very helpful. And
7 most of you should have had communications with
8 them, at least email, and now you can go say hello
9 to them. They're sitting out there, so I won't --
10 Valorie? Come in and let me show people in
11 case they don't know who you are, and to thank you.
12 Valorie Thompson, the young woman with the
13 blonde hair. Valorie is the organizer for this.
14 She is the person that we couldn't do anything or
15 get this set up without her. So thank her for
16 that, and for all the things she's going to do.
17 (Applause.)
18 DR. TURK: Thank you.
19 Any questions that you have about the
20 logistics, about what our intention is? And
21 remember, we're going to herd the cats, so tomorrow
22 you cannot leave -- we will lock the doors -- until

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1 we have a preparation for the manuscript that Jen
2 is able to do. So my flight is late, so I'm quite
3 happy to stay a lot later than some of you. We
4 strongly encourage you to stay through the entire
5 meeting because toward the end is when we sort of
6 come with recommendations, and that's really the
7 critical point for you to be here. So if at all
8 possible, and we know certain times that can't
9 happen.
10 Any questions you have for me? Bob Dworkin
11 is sitting over there, my perpetrator,
12 co-perpetrator. Jen Gewandter, you've seen;
13 Shannon Smith. Rob Edwards, raise your hand and
14 Kushang is not here. Those are the people from
15 ACTTION who have been involved with ACTTION and the
16 development.
17 So thanks to all of them for the work.
18 You'll be hearing more from Shannon and from Gen as
19 the meeting goes on. Rob, I, we have you moderating
20 somebody yet. Okay. So you'll be hearing more from
21 Shannon and from Jen as the meeting goes on.
22 Rob, we have you moderating, so you'll be

Page 19

1 hearing more from him. So I've got through the
2 thank yous.
3 Any questions about the logistics or about
4 what we're about and what we hope to accomplish
5 with this meeting, and what your responsibilities
6 are?
7 (No response.)
8 DR. TURK: That's too easy. No questions?
9 Bob Jamison, nothing to comment? All right.
10 So what I want to do now is I'm going to
11 turn this over to the moderator for this morning
12 session. Kurt Kroenke will be introducing the
13 speakers for the morning. He will also be the
14 chair of the question and answer period. John
15 Farrar was supposed to be doing this with him. John
16 had trouble with his flights.
17 Is he going to get in? So he'll be in
18 later. He may be here in time for some things.
19 He's not here.
20 Kurt, if you want to come up? Some of you
21 may know Dr. Kurk Kroenke, at least most of you if
22 not everybody knows Kurt Kroenke because he's been

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1 around for a long time, as I have. Kurt is a
2 professor of medicine and research scientist at the
3 Indiana University School of Medicine, and he's
4 also from the VA in Indianapolis. So Kurt's going
5 to be the moderator for this session. Any
6 questions you have along the way, by all means, at
7 break time if you have questions for Bob, myself,
8 Jen, Shannon when you're here, and Rob, we'll be
9 happy to answer them.
10 So, Kurt, I'll give you the podium.
11 DR. KROENKE: Yes. So we have a series of
12 30-minute presentations this morning I think by
13 five speakers. There will be a 30-minute break I
14 think after the third one. So it'll be a tight
15 timeline. My only job this morning is to introduce
16 people and make sure people end on time. So if
17 someone's getting close, I'll start waving, and if
18 they're starting to go over, I'll stand, so we can
19 make sure everybody gets -- which means if the
20 speaker ends shortly before the end of the 30
21 minutes, there may be time for a few questions. We
22 won't have 15 minutes of discussions, clarifying

Page 21

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

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

16 Presentation - Eric Strain

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

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

Page 22

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

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

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

Page 23

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

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

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

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

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

17 If you haven't -- I'd just be curious, a
 18 show of hands. Has anybody reading this book?
 19 (Show of hands.)

20 DR. STRAIN: Okay. Great. This is
 21 Dreamland. It's a good 200-page book that lasts
 22 300 pages.

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

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

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

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1 and 2016, and there's the title.
 2 What we have is we have -- just to make sure
 3 it hits home in case you don't -- because it's not
 4 clear in the actual body of the figure. We had
 5 64,000 drug overdose deaths in 2016 in the U.S.,
 6 which is really remarkable. And you've heard all
 7 about how that is relative to auto accidents and
 8 various other ways that people have hurt
 9 themselves.
 10 Along the Y-axis here, we have the number of
 11 deaths. What we see here is -- let me back up.
 12 I'm going to walk you through -- there are
 13 essentially three trends that we're seeing here,
 14 and I'm going to walk you through the three trends
 15 that have been identified with this figure.
 16 The first trend is a slow, steady rise in
 17 prescription opioid overdose deaths. This started
 18 around the year 2000, and you can see it climbing
 19 up there. It's characterized as natural and
 20 semi-synthetic opioids, which in 2016, there were a
 21 little over 14,000 deaths from prescription
 22 opioids. So that was the first trend that we saw.

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

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

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

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

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

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

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

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

4 This translates to a change in the U.S. s
5 death rate. This is all-cause mortality ages 45 to
6 54 for various demographic groups in developed
7 countries. I will again walk you through this.
8 This is deaths per 10,000 on the Y-axis.
9 Basically, what we see is different countries here,
10 and this is U.S. white, non-Hispanics. And you can
11 see that red line is actually trending upwards,
12 which is remarkable. So white overdose deaths are
13 really accounting for that, and there you see it
14 there.

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

1 have a substance-use problem in this country, and
2 we're playing Whac-A-Mole so long as we focus on
3 one drug type or drug class. And I think that's
4 really important to stress. So I think probably
5 everybody in this room knows that there's
6 \$500 million of NIH money for the HEAL Initiative;
7 we're going to take care of opioids. But we have
8 this tendency to focus for a few years on a drug
9 class or a drug problem, and then something else
10 comes up because we become maniacally focused on
11 just one drug problem.

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

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

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

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

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

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1 within a dose, the dose within a prescription, but
 2 not the experience of being exposed to an opioid,
 3 then this probably gets more complicated I think
 4 because I've thought about it.
 5 So as something of an outsider or fish out
 6 of water, let me take you through what I think.
 7 And you guys probably have thought about this a lot
 8 more than I have. So if we decrease the amount of
 9 exposure, first of all, I think we have to
 10 recognize the exposure to an opioid induces some
 11 immediate changes. We know about acute physical
 12 dependence, for example, that there's some
 13 physiologic effect that occurs with just a single
 14 dose of an opioid in naive humans and animals as
 15 well, so maybe it doesn't really matter for the
 16 individual.
 17 It's interesting here because clinical
 18 experience of the first dose by people who go on to
 19 develop an opiate use disorder is they like it from
 20 the start. Not everybody, but a lot of them report
 21 that. If you read anecdotal reports of people of
 22 the first time they ever took heroin or things like

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1 that, what they say is that when they took an
 2 opioid, they felt nauseous. They maybe threw up,
 3 first time in heroin or something like that. And
 4 then they get this warm feeling, and they really
 5 felt good, and they really liked it.
 6 It's interesting that way. So it could be
 7 that there are people where it doesn't matter if
 8 you say, well, we're only going to give somebody a
 9 week's worth of opioids rather than a month's worth
 10 because it may be within that first week they're
 11 going to have that experience that says this is
 12 God's breath on me or things like that. So it may
 13 not matter there.
 14 Second, if we decrease the amount, certainly
 15 there's more typical physical dependence with the
 16 repeated chronic exposure, depending upon what I'd
 17 call the three D's: the drug, the dose, and the
 18 number of days that the person gets it. So we
 19 decrease the risk of physical dependence if we
 20 decrease the total amount of exposure. But then
 21 physical dependence isn't necessarily problematic
 22 use, although physical dependence can run in

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1 parallel with problematic use. And certainly it
 2 becomes more complicated for people who like
 3 opioids when they become physically dependent upon
 4 them under chronic exposure.
 5 Then third, more doses out there runs the
 6 risk of more potential for diversion and misuse.
 7 Here I would note that decreasing availability of
 8 prescription opioids, which appears to be
 9 occurring, is just shifting us to having people now
 10 use heroin and fentanyl. So we've got unintended
 11 consequences. We may be seeing increased opiate
 12 overdose deaths and increased mortality because
 13 we've shut off prescription opioids, and people now
 14 rather than taking a very quantifiable amount of an
 15 opioid are using an unquantifiable amount of opioid
 16 that they get from a dealer.
 17 However, there may be a long-term value to
 18 decreasing the doses out there, so that may have
 19 long-term effects because we decrease the amount of
 20 total exposure, we decrease the number of people
 21 entering the pipeline with an opiate use disorder.
 22 But in the shorter term, we actually may be

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1 increasing the individual and societal costs, such
 2 as deaths, because we're clamping down on
 3 prescription opiate use, which would be part of
 4 opioid sparing.
 5 Opioid sparing could also have other
 6 repercussions. Alternative treatments could be
 7 more expensive to the healthcare system. As I was
 8 saying to Bob or Dennis, I'm on service this month
 9 actually, and working with managed care is just
 10 lousy. If you're in the clinical trenches, you
 11 know. They're not looking for something that's
 12 going to be a more expensive if you offer a
 13 strategy that says, well, I can give somebody
 14 something that will decrease their the risk of
 15 opioid exposure.
 16 Use of another substance could have more
 17 downstream problems either at the individual level
 18 or the societal level. I took out, but I had some
 19 slides when you Google opioid sparing, two of the
 20 top hits are related to cannabis. Everybody now is
 21 sort of on the cannabis bandwagon. And I could
 22 talk for hours about cannabis use because we're on

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1 a grand social experiment there that's not data
 2 driven, not that you might detect my personal
 3 biases on that.
 4 (Laughter.)
 5 DR. STRAIN: But we've got this experiment
 6 that we're engaged in, and we now have a really big
 7 industry, and Canada is going to have an even
 8 bigger one, that is pushing this forward, this
 9 agenda, that the solution to the opioid problem is
 10 to increase availability of cannabis. And we
 11 really don't know what the downstream effects are
 12 going to be of cannabis.
 13 Again, if the ratio is the same but the
 14 exposure is increased, the denominator increases,
 15 the numerator increases, and people do develop
 16 cannabis-use disorder. There's NSDUH data that
 17 suggests about 15 to 17 percent of people exposed
 18 to cannabis develop a cannabis problem. And then
 19 individual efficacy may be lower as we think about
 20 opioid sparing and how that works.
 21 So the bottom line, opioid sparing can have
 22 value for the individual prescribed and for society

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1 I think. Certainly, I'm for it. However, it's
 2 important to note that as we decrease prescription
 3 opiate abuse and exposure, we're seeing a
 4 backfilling with illicit opioid use, for example,
 5 fentanyl. And sparing by itself won't solve the
 6 opioid problem, and it may be actually producing
 7 more societal pain and individual suffering as we
 8 go down this path.
 9 Final thoughts, the value of opioid sparing
 10 likely depends upon the approach used to spare the
 11 opioid. The drive to spare opioid use is good,
 12 it's reasonable. It's hard to argue against it,
 13 especially to lay audiences. And likely, it could
 14 decrease the further development of opioids.
 15 (Loud audio sound.)
 16 DR. STRAIN: My time's up?
 17 (Laughter.)
 18 DR. STRAIN: I have that soporific effect.
 19 And like you can decrease further the
 20 development of opioid-use problems, we have passed
 21 the prescription opioid phase of the crisis.
 22 Overdose deaths are fentanyl, heroin, and

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1 prescription opioids in rank order. And
 2 finally -- and I keep trying to figure out how to
 3 say this, and I'll figure it out eventually. But
 4 the problem did not develop overnight, and the
 5 solution will not be equally quick as a fix,
 6 despite desires to do so and good intentions.
 7 I think that's what worries me the most is
 8 we're going to give \$500 million to NIH, and NIH
 9 should solve this problem in the next 14 to 18
 10 months. I'm looking at Ewan, and Dave, and Kurt,
 11 you guys. And that's not going to be the case. It
 12 took us years to get here, and it's going to take
 13 us years to get out of this problem. And we are
 14 going to now have this larger population with
 15 opiate use disorder that we've got to accommodate
 16 in ways in terms of treatment capacity and
 17 healthcare needs going forward.
 18 So with that, I thank you, and I'm done.
 19 (Applause.)
 20 DR. KROENKE: We have time for a few
 21 questions. [Inaudible - off mic.]
 22 DR. RATHMELL: Jim Rathmell from Brigham

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1 Women. You speak with such wisdom of being in
 2 front of these people who are experiencing this in
 3 reality. Can you speak to someone who's been on
 4 chronic opioids for treatment of chronic pain for a
 5 very long period of time, now faced with
 6 practitioners who will no longer do that, from both
 7 the patient's perspective, the primary care
 8 doctor's perspective and someone like yourself who
 9 might all see the same patient over the course of a
 10 few weeks or months?
 11 DR. STRAIN: One, I think the idea that this
 12 person who's been on a chronic dose of
 13 hydromorphone or morphine, MS Contin or something
 14 for chronic low back pain for years, has done well,
 15 the idea that this person now needs -- I've got a
 16 psychiatric patient I just saw the other day who's
 17 got bipolar II disorder, but he's been on a chronic
 18 dose of oxycodone for years for low back pain, a
 19 stable dose. He gets it from an internist on our
 20 campus.
 21 I think it's nuts to be counseling him to
 22 come off his pain. He's got terrible both knee

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1 pain and low back pain. And he's been stable. He
2 doesn't abuse it. The prescription drug monitoring
3 program doesn't show any evidence of that. His
4 prescriptions are stable that way.
5 DR. RATHMELL: Now they're on 10 times the
6 CDC recommended doses. And it's the same patient.
7 They've been stable. They've been following all
8 the rules. There's no evidence of -- what do you do
9 with that patient when the practitioner is saying
10 I'm getting DEA visits and the like? The same
11 exact scenario, though.
12 DR. STRAIN: Well, I'm not sure, but I would
13 document carefully. That's one of my mantras that
14 I fall back on. Make sure that there's been good
15 documentation about what's been going on in the
16 treatment, why the treatment is necessary, and
17 things like that.
18 Again, I think the prescription drug
19 monitoring programs work to our advantage in that
20 respect because I've got patients I prescribe
21 benzos to certainly, and they're beautiful, the
22 PDMP, at least in Maryland, it shows me every 30

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1 days, or thereabouts, 28 to 32 days, the
2 prescription being filled. And I use that to my
3 advantage in terms of the justification for ongoing
4 use of it. But beyond that I think, I don't know
5 if I've got any wisdom. I have low wisdom.
6 DR. RATHMELL: One last question --
7 DR. KROENKE: [Inaudible - off mic] one
8 question from Brett. I saw a lot of other hands,
9 which means we're going to have a really good
10 discussion at the end. So, Brett, one question.
11 DR. STACEY: This is less of a question and
12 more of a comment, to fess up. I'm Brett Stacey.
13 I'm from the University of Washington. I've known
14 Dennis Turk for a long time.
15 (Laughter.)
16 DR. STACEY: That's okay if he talks over
17 me.
18 DR. STRAIN: Dennis is dementing.
19 DR. STACEY: If we go back to the start of
20 the careers of almost everybody in this room, we
21 were focused on pain treatment, not on substance
22 abuse, and very few people started off as

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1 substance-abuse treaters. And I think part of your
2 talk was excellent, but it was on part of the
3 issue. Part of the issue is the opioid crisis.
4 That's only a small part of the issue.
5 The other issue is that there are
6 dose-related adverse effects for chronic pain
7 patients: depression, endocrine effects, increased
8 likelihood of getting a driving problem, on and on
9 and on, which are separate from the opioid crisis.
10 If all we do is focus on the opioid crisis,
11 we aren't being pain people. We are paying people
12 as well. We want to treat pain, and we want to
13 look at the appropriate role in opioid dosing. So
14 there are a lot of other adverse effects of opioids
15 besides death and besides opioid-use disorder. And
16 that is a much more nuanced and problematic
17 discussion as a couple of people in here can
18 testify to a breakfast discussion about this. So
19 we need to make sure we explore that, too, when we
20 talk about opioid sparing and opioid reduction.
21 DR. STRAIN: Great point. Thank you.
22 DR. KLUETZ: I saw hands up, so I don't

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1 think I'll have to talk much during the moderating
2 session at lunch.
3 Our next speaker is, Dr. Tong Joo Gan,
4 professor and chairman, department of anesthesia at
5 Stony Brook School of Medicine in New York. He's
6 going to be talking about opiate sparing clinical
7 trial objectives and outcomes for acute pain.
8 Presentation - Tong Joo Gan
9 DR. GAN: Good morning. Thank you for the
10 introduction. My name is TJ Gan. I am, as he
11 said, at Stony Brook. I went there four years ago,
12 and before I was at Duke University for over
13 20 years. I'm asked to address on this topic, on
14 opioid-sparing clinical trial objectives and
15 outcomes focused on acute pain. Dr. Katz that
16 follows me later is going to talk about chronic
17 pain.
18 Why am I interested in this topic? Really,
19 I think for two reasons. One is that I'm a
20 clinical anesthesiologist. I see patients, many in
21 the acute pain setting, and we use a lot of
22 opioids, naturally, during surgery, after surgery

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1 to control their pain. As Dr. Stacey was saying,
2 we are pain doctors, and we try to manage pain, but
3 at the same time, we see a lot of opiate related
4 side effects.
5 From my second perspective, as a clinical
6 trialist, I've been involved in many of the
7 analgesics coming on the market over the last 20
8 years, and many of them don't come to the market
9 over the last 20 years, and trying to design
10 studies that would show the value of not only
11 analgesia, but also, on the other hand, the side
12 effects profile. As you know, a drug is on the
13 efficacy and side effects profile, and how can we
14 measure that, and how do we make it as a -- from
15 the patient perspective, how valuable is that?
16 So those are the two aspects that I
17 constantly think about, how can we better manage
18 pain and also manage opiate side effects. And
19 secondly, how do we demonstrate the value of a
20 drug?
21 So let's define the outline that I'm going
22 to talk about. First of all, again, I'll just

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1 introduce some of the opiate adverse events that
2 many of you in the audience are probably very
3 familiar with, so I could probably go fairly
4 quickly, and then talk about the opioid sparing in
5 the context of clinical practice today.
6 As you know, over the last 20 years or so,
7 our pain management is sort of going in circles.
8 At one point, we got pain with vital signs.
9 Everyone should have no pain. The first thing you
10 ask when a patient shows up in clinic is whether
11 you have pain or not; it doesn't matter what their
12 complaints are. Then, too, when we are embracing
13 multimodal analgesia, using them as non-opioids.
14 And more recently in a perioperative setting, with
15 enhanced recovery, a concept that is starting to be
16 embraced. And this is a multimodal,
17 multi-specialty approach to take care of
18 perioperative patients.
19 Within that, we are obviously focusing on
20 managing pain, and I want to share some of the
21 thoughts about how does one assess opiate sparing
22 and how does one assess opioid side effects within

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1 the context of enhanced recovery, which is really a
2 part of clinical practice today, and then briefly
3 talk about assessment of opioid related adverse
4 events, the objective, some of the objective
5 outcomes and some of the more subjective
6 patient-reported outcomes.
7 Now again, this is a study that Jeff
8 Apfelbaum and I undertook a number of years ago,
9 basically just simply asking patients about their
10 pain experience after surgery. I didn't show you
11 the slide on the incidence of pain, but the gist of
12 it is that many of our patients have pain
13 postoperatively. Over 50 percent of our patients
14 said their pain was either severe or extreme at
15 some point after surgery, within 6 weeks after
16 their surgery.
17 When we ask them, tell us a little bit about
18 your side effects that you experienced, we didn't
19 mention anything about opioids, but just tell us
20 about some of the things that you experienced that
21 you did not like to experience. And this is the
22 list of symptoms from the patients who said at some

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1 point after surgery, these are some of the side
2 effects.
3 Now, if you go down the list, you can see
4 that almost everyone could potentially be related
5 to opioid side effects: drowsiness, nausea,
6 constipation, dizziness, vomiting, you name it. So
7 clearly, opioid side effects are very, very common.
8 We all know that opioids that unrelieve pain
9 post-surgically can have problems from inadequate
10 or increased sympathetic tone resulting in
11 increased oxygen demands, and in patients who are
12 already teetering at a border can potentially
13 develop ischemic heart disease and myocardial
14 infarction. We also know that if they can't
15 breathe deeply, they potentially can get chest
16 infection resulting in pneumonia, and also
17 obviously they can't have a good sleep, especially
18 after surgery, if they have pain. So there are
19 many reasons to want to treat pain.
20 We also heard that now with the opioid
21 crisis -- and I'm not going to talk more about that
22 but just to say recently there were studies

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1 suggesting that in fact 1 in 10 patients reported
2 become addicted to opioids following surgery.
3 These are situations where I'm sure many of you are
4 familiar with. You had a minor procedure, and you
5 are being sent home with 60, 90 pills of Percocet,
6 Vicodin, and most of the people take about 3 or 5,
7 and they kept the rest in their medicine cabinet to
8 be helped by friends and relatives who come and
9 visit. So clearly, it is a problem, and it is
10 something that we are solving.
11 The other interesting thing about opioids
12 and side effects is that we sometimes don't realize
13 how much impact it has on the cost of healthcare
14 delivery on the length of hospital stay. This is a
15 study that we published a few years ago using the
16 PRIMIER database, just looking at the patient
17 discharge with an opiate related adverse events and
18 compare to those patients without an opiate related
19 adverse events. And as you can see, those who had
20 opiate adverse events not only had an increased
21 length of stay, but also the costs of that hospital
22 admissions.

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1 So clearly it's expensive to have the opiate
2 adverse events following surgery.
3 Now, we also know there's increasing
4 evidence that patients stop using opioids after
5 minor or major surgical procedures. this is a
6 recent study that shows about 8 to 10 percent usage
7 of opioids following an acute episode, and they
8 continue to use opioids in some of the major
9 procedures. A colectomy is even higher. So
10 clearly, if we can avoid that, potentially we might
11 be able to reduce the problem of prolonged opioid
12 use.
13 Opioids within the hospital also can be
14 deadly. This is a study that Frank Overdyk and I,
15 we looked at, again, the PRIMIER database, looking
16 at an incidents of cardiorespiratory pulmonary
17 arrest in the hospital. And we looked at both
18 surgical and medical patients, and clearly there
19 are many patients who are on opioids. Many
20 patients are on sedatives. The rate of
21 cardiopulmonary respiratory arrest is listed down
22 here, and you can see medical patients and surgical

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1 patients.
2 Now, if you have opioid and sedative in
3 combination, your rate of cardiopulmonary
4 respiratory arrest goes up substantially, in this
5 case almost about 4 times. And if you do a
6 multivariate analysis, again, whether it's surgical
7 or medical patients, typically if you add sedatives
8 and opioids together, your rate of cardiopulmonary
9 arrest goes up at least twice. So clearly, it is
10 something that we could potentially better manage
11 by either reducing opioids and maybe better
12 monitoring. So certainly, there are a number of
13 strategies there.
14 Clearly, treating pain is a balancing act.
15 On the one hand, you under trying to reduce pain;
16 on the other hand, you are trying to manage the
17 side effects of the drugs that you use.
18 Now interestingly, from the patient
19 perspective, if you were to ask patients what do
20 you really want in terms of pain management, what
21 would make you happy after surgery in terms of pain
22 management, you would think that, well, I want to

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1 have zero pain. But in fact, it turns out that is
2 really not the case.
3 This study we conducted a few years ago,
4 really asking patients who are on PCA, on opioids
5 PCA, we asked them what are the things that make
6 you decide to press that pain button? Many of you
7 who do pain rounds, you go to see Ms. Smith that
8 complain 10 out of 10 pain. And Ms. Smith has a
9 PCA button in her hand, and she hasn't pressed the
10 button for the last 2 hours.
11 You go to Ms. Smith and say, Now, I
12 understand you complain of a 10 out of 10 pain.
13 You know that you have that pain button in your
14 hand that's supposed to treat your pain. She says,
15 "I know. I've got a pain button." I say, "Why
16 haven't you pressed it in the last hour or so?"
17 Then you begin to hear from Ms. Smith the reasons
18 that determine her pressing the button versus not
19 pressing the button.
20 So when we're presented with a scenario
21 about -- let me give you two scenarios. One
22 scenario is where you have good pain relief but it

1 comes with moderate vomiting versus just for pain
 2 relief, not quite as good but no side effects. And
 3 you can see the majority of patients actually
 4 prefer not having the side effects and managing
 5 somewhat some degree of pain. "I don't necessarily
 6 need to have no pain."
 7 Likewise, another scenario, severe
 8 constipation with excellent pain relief, great pain
 9 relief, but you can't open your bowels, versus just
 10 good pain relief with mild constipation. And
 11 again, the majority of patients -- as you can see,
 12 from the patient perspective, they would rather
 13 avoid the side effects because they know that these
 14 side effects are annoying, nausea. Ms. Smith says,
 15 "Well, when I press the button, they make me feel
 16 drowsy, they make me feel loopy, and I just don't
 17 like it." So they trade off between efficacy and
 18 the side effects profile, and that's what we do all
 19 the time.
 20 Now, we know there are a number of
 21 non-opioid analgesics. As you know, pain coming
 22 from peripheral to the central up to the brain at

1 the patient is in pain." But the patient has a
 2 good working epidurals. So sometimes you've got to
 3 think about how do we best give opioids
 4 interoperatively and postoperatively.
 5 So what are the objectives that we are
 6 trying to accomplish in a patient having major
 7 surgery, trying to manage their pain? I think
 8 there are really three aspects. One is to keep
 9 patients comfortable, to try to make sure that they
 10 are at a level they can actually go about either
 11 doing their rehabilitation. They can get out of
 12 bed and walk around, and they are able to sleep at
 13 night.
 14 So to keep them comfortable and at the same
 15 time trying to encourage recovery because they're
 16 not going to be staying in a hospital for a long
 17 time. And nowadays, most surgical procedures,
 18 either they are done on the same day or they stay
 19 one night, or a couple of nights. It's rare for
 20 patients to stay in the hospital for 5, 6, 7 days
 21 at a stretch. I think we have better surgical
 22 techniques. We manage pain better. And we want to

1 the same time, at every point in time or every path
 2 of that pain pathway, there are certain non-opioids
 3 that certainly can be effective, local anesthetic,
 4 nonsteroidal, as well as the alpha-2 agonists, and
 5 obviously some of the other drugs, ketamine and
 6 acetaminophen. So there are a number of
 7 non-opioids that we can use to minimize the amount
 8 of opioids.
 9 So the question is this, how can we better
 10 effectively treat pain? And again, certainly now
 11 with regional anesthetic techniques that we
 12 employ -- and if you are having a good block, you
 13 really don't need anything else. For example, if
 14 you have a good working epidural, there is really
 15 no need to add additional opioids. But we always
 16 seem to think that we need some opioids
 17 interoperatively.
 18 I often walk into the room where either
 19 nurse anesthetist or residents, they give 50 mgs of
 20 fentanyl every half an hour. And they say, "Why do
 21 you do that for?" "Well, you know, pressure goes
 22 up a little bit and heart rate goes up. I think

1 get them out quicker with this enhanced recovery
 2 concept, at the same time minimizing the side
 3 effects.
 4 So I think this concept about encouraging
 5 postoperative dreams -- what does postoperative
 6 dreams stand for? Well, dreams stand for drinking,
 7 eating, analgesia, mobilizing, and sleeping. Now,
 8 if you can do all of these 5 things, number 1, the
 9 patient can get out of the hospital; number 2, then
 10 you have a good surgical recovery. And this is
 11 what is enhanced recovery concept, trying to
 12 promote getting the patient up and about as soon as
 13 possible, have a reasonable good management of pain
 14 to reduce some of the side effects, get them to eat
 15 and drink, and get out of the hospital.
 16 I just want to share with you in this
 17 context of enhanced recovery, I think it is now
 18 starting to become I believe the standard of care
 19 in the U.S. In fact, it has been done in many
 20 other countries.
 21 This is a study that we did at Duke,
 22 basically just to look at how does integrating the

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1 enhanced recovery program help our postsurgical
 2 patients. We looked at colorectal patients
 3 undergoing colorectal surgery, either open or
 4 laparoscopic. This is our analgesic regimen here.
 5 We did a thoracic epidural, an open tap block for
 6 the laparoscopic approach, and a variety of a
 7 non-opioid multimodal analgesics, together with
 8 antiemetic prophylaxis, and using that as a
 9 management strategy and trying to reduce
 10 intraoperative and postoperative opioids.
 11 Again, this is not just pain control. There
 12 are other aspects with enhanced recovery, but we
 13 did see a significant reduction in length of stay
 14 on average, about 2 days, even for laparoscopic
 15 procedures.
 16 Now, if you look at pain specifically and
 17 opioid sparing, on the left side of the graph here
 18 shows you the amount of morphine equivalent during
 19 surgery and after surgery. And again, you can see
 20 that with a multimodal approach of pain management,
 21 with a good working regional thoracic epidural or
 22 tap block, we can significantly reduce the amount

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1 of opioids I give patients.
 2 Now, the other interesting -- that we found
 3 was that you often hear surgeons -- any surgeons in
 4 the room here? You always hear surgeons say
 5 laparoscopic procedure is a minor procedure, and it
 6 doesn't hurt. Right? There's no need to give any
 7 analgesic. But interesting, when we looked at the
 8 degree of pain, there is really not that much
 9 difference between the open approach and the
 10 laparoscopic approach. The duration may be
 11 shorter, but the pain intensity is actually pretty
 12 intense, even though with the little keyhole
 13 surgery.
 14 Again, the enhanced recovery group had a
 15 better pain score. I just want to focus that in
 16 terms of bowel recovery, again, minimizing opioids
 17 enhances bowel recovery because we short opioid
 18 reduction by about fourfold in the enhanced
 19 recovery group.
 20 So the last part of my talk is to really
 21 look at how can we assess this opioid sparing. And
 22 I think it's a question that we don't really have a

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1 good answer. There are really two ways that you
 2 can assess opioid related side effects and opioid
 3 sparing.
 4 What is the impact of opioid sparing? Now
 5 again, reducing 30, 50 milligrams of morphine
 6 equivalent isn't really a big deal. Right?
 7 Opioids, morphine is inexpensive. Fentanyl is
 8 inexpensive. But what is more important is can you
 9 demonstrate a corresponding reduction of side
 10 effects, which I think is much more difficult to
 11 treat. And also, those are the ones that prolong
 12 the hospital stay, and patients tell us that they
 13 don't like it.
 14 So there are objective and subjective ways
 15 to assess that; objective, certainly in the
 16 incidence of vomiting, time to GI recovery, and the
 17 need for any rescue medication for opiate adverse
 18 events. So these are fairly objective.
 19 Then there is also from the subjective
 20 perspective, from the patient-reported
 21 outcome -- which certainly is important because
 22 this is what patients tell us that they like or

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1 dislike. There are a number of scoring systems
 2 trying to assess that on the patient-reported
 3 outcomes of opiate related side effects, and I just
 4 want to run through some of these with you.
 5 So one of these is this postoperative
 6 Opiate-Related Symptom Distress Scale, which was
 7 originally developed in chronic pain by Russ
 8 Portenoy. A number of years ago we thought, well,
 9 could we adapt it in the acute postoperative
 10 setting. And when we are doing the Cox-2 trials
 11 and we're trying to validate this instrument -- and
 12 essentially, this instrument looks at opiate
 13 related adverse events: nausea, vomiting,
 14 constipation, diarrhea, difficult passing urine,
 15 some of these post-op events that patients may
 16 experience.
 17 We collected the data over the next 10 days
 18 after surgery and really just tried to see is that
 19 a good instrument to demonstrate opiate sparing,
 20 and more importantly opiate related adverse events.
 21 So we did a validation study. For the
 22 scale, we measured 3-dimension. We measured the

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1 frequency of the adverse events, how frequently
2 does it happen; how severe was the adverse events,
3 if you have either minor nausea or very severe
4 nausea; and how much does it bother the patient
5 because some side effects may not bother the
6 patient that much; so I think this degree of what
7 is the bothersomeness of the side effects.
8 We looked at these three dimensions, and
9 patients tell us over the postoperative days after
10 surgery and showed that they correlated with the
11 opioid reduction on opiate doses. If you were to
12 plot -- this is over 10 days after surgery, and
13 this is the clinically meaningful events, so these
14 are a combination of frequency, severity, and
15 bothersomeness, and this correlates with opioid
16 consumption.
17 Certainly, if you look at opioid consumption
18 here in the open circle, probably within the first
19 3 to 4 days, this is where most people consume most
20 of the opioids. Beyond that -- and again, these
21 are patients undergoing lap chole. So beyond that,
22 most of the people just tail off, do not really

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1 need that much opioids. And again, you can see the
2 adverse events frequency correlate pretty well with
3 the opioid doses.
4 So perhaps this could be an instrument to
5 try to assess the degree of opioid sparing and also
6 what does it mean from the patient perspective.
7 Now, there are other patient-reported scores
8 that have been validated and published. There is
9 the quality of recovery score, and there are 15
10 questions and another version with 40 questions by
11 Paul Malz [ph] and his group from Australia,
12 essentially looking at not just opioid adverse
13 events but the general recovery in terms of how
14 well you sleep and how do you interact with your
15 friends and relatives. So again, that has been
16 validated as a postoperative recovery
17 patient-reported outcome scoring system.
18 More recently, a group came together to look
19 at all the trials that have been published related
20 to patient-reported outcomes. Using a modified
21 Delphi technique, we went through a number of
22 iterations to look at what are the things that we

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1 felt that, first of all, is valid as a scoring
2 system. Is it reliable? And more important, is it
3 feasible to be done in a clinical setting? And
4 what does it mean to the patients?
5 So we went through this iteratively and then
6 scored this between zero and 10. So the higher the
7 score means the more validity and more feasible it
8 is to collect, and more patient centered
9 [indiscernible] is the score. Again, pain is
10 certainly an important outcome that patients care
11 about. Nausea and vomiting are other ones that
12 postoperatively happen commonly, and I think is
13 something that's important to avoid; the quality of
14 recovery score as well as time to GI recovery
15 because that also predicts the length of stay; the
16 time to rehabilitation and mobilization because the
17 earlier you can get a patient out of bed usually
18 means they can get out of the hospital.
19 Now, if you were to go and visit your
20 patient postoperatively, those patients that stay
21 in the hospital, you will find that about 50
22 percent of the time, the reason they occupy a

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1 hospital bed is because their bowel is not working.
2 When a bowel is not working, they ain't going
3 anywhere; they stay in the hospital. But as soon
4 as bowels start to move, that is when you are able
5 to discharge patients usually the next day. And
6 obviously, the other aspects, sleep is also
7 important.
8 Many professional societies, including the
9 American Society of Anesthesiology, advocate this
10 concept of the multimodal approach, giving
11 non-opioid analgesics. We know that it works. We
12 know that it can potentially reduce opioids. In
13 fact, with the enhanced recovery protocol,
14 advocating not only multimodal but also reasonable
15 technique, a number of procedures now can be done
16 without opioids. Opioid free is certainly
17 achievable if you've got a good regional block, and
18 then post operatively you can probably just get
19 away with nonsteroidal or either non-opioids.
20 So the challenge is how does this translate
21 into a company who wants to approve an analgesic
22 and demonstrate the value of non-opioids? This is

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

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

13 (Applause.)

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

16 (No response.)

17 DR. KROENKE: Okay. Thank you.

18 DR. GAN: Thank you.

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

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1 and outcomes for chronic pain.

2 Presentation - Nathaniel Katz

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

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

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

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

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

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

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

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

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

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1 meaning insofar as we can show some direct patient
2 benefit of that opioid dose reduction? Or do you
3 need both, some combination of both?
4 So that's scenario number 1 and the benefits
5 of what we can learn and that scenario, but also
6 some of the kind of philosophical challenges posed
7 by that scenario.
8 Let's talk about a second scenario, scenario
9 2 here. Patients with chronic pain are coming in
10 on some substantive doses of opioids already. And
11 again, as in the first scenario, you're randomizing
12 them to some non-opioid analgesic regimen. You're
13 trying to take over some of the pain control that
14 those opioids are presumably providing to those
15 patients, compare it to some placebo or some
16 control condition.
17 But here, in contrast to the first scenario,
18 you're trying to get people off their opioids or at
19 least trying to lower their doses. And you're
20 doing that by using some other treatment to
21 maintain their pain control. So the hypothesis
22 that can be addressed in a study like that is that

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1 the patients on the analgesic arm can lower their
2 dose.
3 So now you're talking about maybe mean dose
4 between the two groups at the end of the study or
5 you can get some certain percentage of patients
6 off. So maybe 40 percent of the patients in this
7 arm came off, but only 10 percent of the patients
8 in that arm came off. And you have this concept
9 that we all resonate with, that the patients don't
10 need opioids anymore at all, and Eric alluded to
11 that as well.
12 So that brings us to another philosophical
13 question that we'll have to deal with, which is do
14 we think of the concept of opioid sparing
15 differently if I just lower your dose versus if I
16 get you off completely? Is getting you off
17 completely enough in terms of opioid sparing? Is
18 that by itself intrinsically an accomplishment or
19 do I have to show that I've actually reduced your
20 nausea or constipation or something like that?
21 I think what I would put on the table for
22 your consideration is that I think getting people

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1 off of opioids has intrinsic value. Although,
2 again, we get back to this concept that we have to
3 keep a grasp on, which is that getting people off
4 their opioids or lowering their doses doesn't
5 really have any value to the patients unless we're
6 maintaining their pain control, as Eric said
7 earlier.
8 That seems like a really obvious concept to
9 me, at least as a clinician, but you'd be surprised
10 how hard it has been to convince some
11 pharmaceutical companies that just lowering your
12 opioid exposure but letting your pain get out of
13 control, that doesn't actually have value to the
14 patient. And a number of companies have gone
15 pretty far along the clinical development path
16 until they finally crashed and burned because of
17 the obviousness of that issue.
18 So as we define opioid sparing, we're going
19 to need to consider whether sparing somebody their
20 opioid dosage is meaningful unless we're also
21 sustaining their pain control. And personally, I
22 think it's not.

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1 Scenario number 4, here we bring patients in
2 with chronic pain and we put them on some standard
3 opioid, and then we're developing some better
4 opioid. What does better mean? Better means maybe
5 something like it can give them just as good pain
6 control but fewer side effects. That would be a
7 huge societal benefit.
8 As TJ mentioned earlier, in the chronic pain
9 setting, as in the acute pain setting, patients are
10 usually trading off some degree of side effects for
11 some degree of benefit. The patient who is
12 absolutely free of side effects, I don't think I've
13 ever seen that patient in the chronic pain a
14 setting. There is always some degree of side
15 effects. If there was some better opioid, that
16 would be great.
17 So here, it's not about dose in this
18 scenario. This scenario doesn't care about the
19 dose. This scenario cares about the patient and
20 whether the patient maintain, has a better
21 therapeutic index of their opioids; let's just say
22 same pain control but fewer side effects.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 enhancing thing that that modifies the
 2 pharmacology.

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

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

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

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

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

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

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1 So this is a definition of opioid sparing
 2 that deliberately is not just focused on reducing
 3 the dose, but we may decide as a group to reject
 4 that.
 5 Now to the question of what are -- now I'm
 6 going to extend TJ's comments about acute pain to
 7 the chronic pain setting, and what actually are the
 8 adverse effects of opioids that we might want to
 9 measure if we're going to claim that we've reduced
 10 them.
 11 First is the individual, what you might call
 12 the nuisance side effects, although too many
 13 patients, that's a lot more than a nuisance.
 14 Vomiting all day is not fun. And actually, as TJ
 15 said, you'd prefer more pain for less vomiting in
 16 many situations. So there's the long list that TJ
 17 mentioned: nausea, vomiting, et cetera, et cetera.
 18 Now here's a very important conceptual
 19 point, and this is probably the most important
 20 thing that I'm going to bring to your attention
 21 during my presentation. So if you're going to just
 22 pay attention to one issue during my presentation,

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1 this is the one to pay attention to, which is are
 2 opioid side effects as a whole one thing, or are
 3 they actually a mish-mosh of different things?
 4 So is nausea, nausea; and vomiting,
 5 vomiting; and dizziness, dizziness; and sedation,
 6 sedation; and we have to measure each one
 7 individually and show that when we are reducing the
 8 burden of opiate adverse effects, we have to be
 9 specific about which one we are reducing and which
 10 one we're not; or can you consider all of these
 11 things together as one thing?
 12 Are we reducing opioid related side effects,
 13 and what are the implications of that? And I think
 14 the people in the room who are wondering about this
 15 know who they are. So this is very important
 16 because if you don't believe that opioid side
 17 effects are a single thing, then talking about we
 18 reduced opioid side effects, that has no meaning
 19 and probably wouldn't end up in a package insert, I
 20 wouldn't think, because we don't like meaningless
 21 things in package inserts; whereas, if you think
 22 that they're all individual things and that each

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1 one's going to have to be dealt with on their own.
 2 So this is an important conceptual issue
 3 that I will dwell on it at some length in the next
 4 one or two slides.
 5 Back to the list of what the opioid adverse
 6 events are in chronic pain. Endocrinopathy, I
 7 think probably most people are familiar with that
 8 these days, but this is actually probably the most
 9 common serious toxicity of long-term opioid
 10 therapy, the endocrinopathy, although it's the
 11 lowest on the list in terms of what people talk
 12 about.
 13 This probably occurs in the majority of
 14 people on long-term opioids; not the minority, the
 15 majority. If you care about things like
 16 infertility and sexual function, then you care
 17 about endocrinopathy -- and osteoporosis and
 18 compression fractures, then you ought to care about
 19 this, but it actually has gotten very little
 20 attention.
 21 TJ mentioned overdoses already; this is a
 22 big problem. And then the panoply of problems that

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1 fall under the abuse and addiction. This is also
 2 not exhaustive, but it's a list of the major kind
 3 of categories of adverse effects of opioids that we
 4 worry about in the chronic pain setting.
 5 So let me get to the issue of whether the
 6 opioid side effects are one thing or they're just a
 7 jumble of different things. When I say one thing,
 8 the word that comes to mind is -- we already have a
 9 word for that, which is "syndrome." This is the
 10 Merriam-Webster definition of a syndrome, which is
 11 a group of signs and symptoms -- it can be signs;
 12 it can be symptoms -- that occur together and
 13 characterize a particular abnormality and
 14 condition.
 15 It has a lot of impact on measurement. I'll
 16 give you an example. The WOMAC pain subscale is an
 17 example. You've got 5 items there. That pain
 18 subscales is accepted as a validated measure of one
 19 clinical concept, which is the pain in patients
 20 with osteoarthritis, the hip or a knee. But the 5
 21 items are asking people about different things.
 22 One is pain on activity. One is pain on standing.

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1 One is pain on sleeping. One is pain walking up
2 and down stairs.
3 So you're measuring one concept, which is
4 pain in osteoarthritis, but you're measuring
5 it -- it's classical test construction theory. You
6 measure it most reliably by asking patients about
7 different manifestations of that same underlying
8 concept. Pain on sleeping is not the same as pain
9 on walking on a flat surface. Those are different
10 things, but they're thought to be measures of the
11 same underlying concept.
12 But if you're talking about something like
13 the WOMAC scale in its entirety, you're talking
14 about one group of items that measures pain; one
15 group of items that measures stiffness, which is a
16 different thing, different concept; a third set of
17 items that measures physical function. That's a
18 different thing, and you don't add them up. You
19 don't combine them because they're not measuring
20 the same concept.
21 So from a measurement perspective,
22 psychometricians are always grappling with this

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1 issue, is what does it mean to have different
2 questions that measure the same thing or different
3 groups of questions that measure different things?
4 So back to the opioid thing, it's obvious
5 that you have the same issue here. Are all these
6 things one underlying concept or are they just all
7 different things that cannot be combined into a
8 single measure?
9 Now, TJ has already answered this question
10 from the perspective of acute pain, which is that
11 they have developed a scale of opioid related side
12 effects, which you wouldn't have developed a scale
13 like that unless they were all measures of the same
14 thing, and I'll deal with that a little bit
15 further.
16 Now, because this issue is so important,
17 even though my time is going by quickly, I'm going
18 to try to give like a warm and cozy example of this
19 to get people comfortable with the concept of
20 different elements of a syndrome because it's more
21 controversial with respect to these opioid side
22 effects.

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1 Here's another syndrome, a collection of
2 signs and symptoms that are all different aspects
3 of one underlying process, which is the acute
4 opioid abstinence syndrome, opioid withdrawal.
5 Some people get nausea, some people get stomach
6 cramps, some people get muscle twitching. These
7 are 10 of the core features of this syndrome. And
8 in fact, these are the items on the SOWS gossip
9 scale of measuring opioid withdrawal, which became
10 a scale because these are the cardinal
11 manifestations of opioid withdrawal.
12 So if you do factor analysis, blah, blah,
13 blah, you'll learn from a psychometric perspective
14 that these in fact can be considered different
15 elements of the same syndromes. If I add all these
16 things up and create a score, and I do a clinical
17 trial where, gee, in this group, the opioid
18 withdrawal was less than this group, if you add
19 these things up and the overall score is less in
20 one group than another, you would say that that
21 group had less opioid withdrawal.
22 Does that mean that feeling cold was reduced

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1 compared to one group, or that yawning was reduced,
2 or that aches and pains was reduced? Not
3 necessarily. Some people will have less nausea.
4 Some people will have less aches and pains. But if
5 you add up their opioid withdrawal score, they have
6 less opioid withdrawal, and that's accepted as a
7 concept.
8 In fact, you could take this even further
9 and you could imagine that maybe there's some drug
10 that reduces opioid withdrawal, and clearly the
11 opioid withdrawal scores are lower in one group
12 than another, and statistically significant, and
13 clinically significant, and all that stuff. But
14 maybe because of the nature of that one drug, it
15 actually really doesn't reduce. I don't know
16 what's a good example. Palpitations? Maybe it
17 actually produces tachycardia as one of its side
18 effects, and maybe palpitations would be even worse
19 in the group with less opioid withdrawal than the
20 other group, and maybe even that would be
21 statistically and clinically significant if you
22 picked out that one item.

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

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

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

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

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

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

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

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

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

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

22 You'd be shocked and appalled at how many

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 Presentation - Sharon Hertz
 2 DR. HERTZ: I'm not going to talk about the
 3 regulatory aspects of this.
 4 (Laughter.)
 5 DR. HERTZ: It's just a handy placeholder
 6 because I'm always behind on getting things to the
 7 organizers. So sorry about that. I'm just going
 8 to share some thoughts about what comes up when we
 9 hear from sponsors who are interested in this and
 10 some of the things that we think about. We don't
 11 really have a formal -- well, we kind of have been
 12 providing advice, but we're working on a guidance.
 13 That's the big news. And it's going through
 14 clearance. So everybody in this room will have an
 15 opportunity to comment on this when it goes out for
 16 public comment. Yay! So you'll all be ready to
 17 provide us with the help we need to make this a
 18 better guidance by sending us comments to the
 19 docket.
 20 A lot of this you've heard in great detail
 21 today. The critical questions really are why even
 22 bother sparing opioids? I know this may sound a

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1 little heretical, but they're perfectly good
 2 analgesics. So why do we need to spare them? And
 3 there's a variety of reasons that we've heard.
 4 People are troubled by adverse events. You've got
 5 a lot of information on that. We worry about
 6 people overdosing, and we worry about people
 7 developing addiction.
 8 What about the general societal concerns?
 9 This is always a challenging one for us because we
 10 have been legislated to taking societal concerns
 11 into our regulatory decisions, because until it was
 12 legislated, we never thought about anybody except
 13 the single patient involved.
 14 So anyway, we worry about the overall
 15 benefit to patients. We look at it in the context
 16 of the greater picture of public health, and we
 17 know from a variety of surveys that the opioids
 18 that are being abused in the community, the
 19 prescription opioids, part of it, are often
 20 obtained ultimately from a physician, whether it's
 21 the patient or more commonly not the patient who
 22 ends up abusing the drug.

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1 Here's the interesting thing. Perhaps some
 2 of you are already aware of that. But what does
 3 industry think, and how do we respond to these
 4 different proposals? I would say that the most
 5 common proposals we see involve the two dreaded
 6 words, "statistically significant," which really is
 7 helpful in terms of understanding what happens by
 8 chance, as you all well know, but may have very
 9 little relevance for an actual clinical outcome
 10 benefit.
 11 So we've had everything from, simply, well,
 12 there's a difference in the amount that's being
 13 taken; let's look at it as a percent reduction.
 14 That's a great way to exaggerate a clinically
 15 meaningless difference.
 16 (Laughter.)
 17 DR. HERTZ: And let's look at the number of
 18 doses -- I actually have an interesting example for
 19 that -- and the percent of patients opioid free.
 20 And that's actually an interesting concept because
 21 when are they opioid free? Are they opioid free
 22 post-op, but then they go home with 600-milligram

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1 oxycodone, or are they opioid free for their entire
 2 acute pain recovery? And then there's also more to
 3 worry about with chronic pain, which you've heard
 4 about.
 5 So we often struggle with the concept of
 6 clinical meaningfulness. And this group has over
 7 the years struggled with trying to define
 8 clinically meaningful differences in a variety of
 9 settings, and it's really hard to do for all the
 10 reasons that we know about. It's all relative, and
 11 we always have to look at clinical meaningfulness
 12 in the context of benefit and risk.
 13 So it's great if you can reduce the opioids
 14 but not if you lose your liver in the process. And
 15 I can spare opioids pretty easily by denying them
 16 to patients, which is apparently an all too common
 17 phenomenon these days, but that's not achieving the
 18 goal of managing a patient who has pain in a
 19 clinically responsible manner.
 20 So these are some of the questions. How
 21 much of a reduction is important? And I dare say
 22 that we will never have an absolute number to

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

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

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

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

6 These are the kinds of data we get, and
 7 these are the data that underlie some of our
 8 conversations about what is a valuable
 9 opioid-sparing outcome. Here we have an AUC for
 10 numerical rating scale or a VAS, visual analog
 11 scale, depending on the studies. We have two
 12 different doses in the two different studies. We
 13 have two different evaluation periods. The first
 14 study was a 48-hour period. The second was a
 15 72-hour period.

16 We can see the AUC, some pain intensity
 17 difference in the first row. We can see the total
 18 amount of opioid use converted into morphine
 19 equivalence. This is obviously post-op. And there
 20 are two things that are quite different. In
 21 study 327, we have the active arm used, on average,
 22 25 milligrams of morphine versus 113 in the placebo

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

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

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

15 (Laughter.)

16 DR. HERTZ: I'm only raising questions.

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

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

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

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

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

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1 studies of two different doses of drug A plus
 2 placebo.
 3 I like medians a lot in addition to means,
 4 so I always push for them because I think here it's
 5 very telling, especially when you look at the
 6 range. This was a pretty varied population. Some
 7 people were using 184 tablets per month at
 8 baseline. This was clearly not the same as the
 9 person using zero. And just averaging that
 10 together made absolutely no sense to me. It also
 11 shows it's fairly balanced at baseline.
 12 Let's look at what happened at month 3. The
 13 higher dose of drug A dropped by an average of
 14 5 tablets a month. Okay. That's good. The median
 15 went down to zero. Well, that's interesting, but
 16 the maximum actually went up for a couple of people
 17 and stayed fairly stable for those high-end people
 18 who were using more tablets per month.
 19 Here's some more data from this. These are
 20 actually in the PI. I just don't know if it's gone
 21 public yet. I think the product was approved.
 22 Here we have the number and percent of patients on

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1 an opioid at baseline who went off the opioid at
 2 3 months. So how many people no longer needed to
 3 use opioids on a regular basis?
 4 Here, well, those are a little bit more
 5 interesting because it kind of tells us something
 6 other than these odd pill counts, which I think was
 7 useful. But here, we sort of see a difference. So
 8 we have a bigger number in the active groups than
 9 the placebo, but a fair number of the placebo
 10 patients went off their opioid as well, but then
 11 what's the converse?
 12 How many people who started off not
 13 requiring opioids ended up on some opioids by the
 14 end of the study? Because there's this natural
 15 history to this process as well. And lo and
 16 behold, yeah, some people ended up going on who
 17 hadn't been on before, not as many who went off.
 18 And in the first study, there was a little bit of a
 19 difference, and in the second study, it was a
 20 little bit more.
 21 So, I don't know. Is this drug opioid
 22 sparing? I think it would be more telling if we

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1 actually had pill counts in association with this
 2 as well. But if we go back to here, if on average
 3 the population reduces the number of pills per
 4 month by 3 or 8, I don't know. If you still have
 5 people using almost 200 pills over the course of a
 6 month, is that opioid sparing? I told you I wasn't
 7 going to answer any of that.
 8 This drug was not approved. Here is some
 9 information. This drug product's whole reason for
 10 existing was presumably going to be a better
 11 adverse event profile than the two opioid
 12 comparators that were studied. Here are two
 13 studies. There was a low-dose study and a
 14 high-dose study. Here's the general adverse event
 15 profile, one of the things that Nat mentioned, as
 16 one way to consider looking. And you can kind of
 17 see things are a little higher, a little lower.
 18 It doesn't look especially different, at
 19 least to me. The high dose, opioid 1, maybe looked
 20 the best in some things. It was less constipating,
 21 but, again, it was a low percentage, and the high
 22 dose study was much smaller. So I don't know.

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1 This overall doesn't look particularly informative
 2 as to opioid sparing, but it depends.
 3 Then what about supplemental oxygen use
 4 because that's a big issue if you're having
 5 respiratory depression. This is post-op. That
 6 would be great to try and reduce the risk of
 7 post-op respiratory depression. And this table is
 8 kind of wacky because what we did was we kind of
 9 smushed things together because some studies had
 10 different dosing arms.
 11 The gray boxes just show that, for instance,
 12 in study 1e, there was all high dose. And if you
 13 look at that, the supplemental oxygen use as one
 14 possible measure for a benefit didn't pan out. So
 15 is this the right measure? What if we looked at
 16 oxygen saturations? What's the trigger for using
 17 supplemental oxygen? Should we have looked at some
 18 other measure?
 19 In the low-dose group, maybe, I don't know,
 20 it was just really hard to tell what -- it looks
 21 like my percentages are a little off on some of
 22 that. Anyway, this is the kind of thing that a

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1 study -- now, I have to say that there were many
2 measures of evaluating respiratory depression in
3 this study, and it did include things like pulse
4 oximetry and a variety of things. And at the end
5 of the day, this one didn't really show an effect.
6 But this was one way of trying to evaluate it, and
7 unfortunately for this sponsor, drug B didn't do
8 what it hoped would happen.
9 That's why I have in terms of slides. I
10 couldn't find some of the other studies that I was
11 looking for last night. If you look at some of our
12 labeling -- and I'm sorry that I didn't put these
13 up -- we do have some information in labels about
14 the amount of rescue opioid use. And we use it in
15 a variety of different ways.
16 For instance, for pediatric analgesic
17 studies, especially for the very young, we don't
18 really use placebos. We use an add-on design. So
19 the amount of opioid use is really the primary
20 outcome measure. It could be adding an opioid to
21 an opioid. It could be adding a non-opioid to an
22 opioid. There are all kinds of combinations.

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1 For the parental acetaminophen and the
2 parenteral ibuprofen, we have some information in
3 there. Also, these were older programs, and they
4 even have some information about the relative
5 amount of opioid used in the studies in adults. It
6 also says we don't know what it means because there
7 were some differences. But that was all we had was
8 numeric differences. We didn't have anything else
9 to go with it. So we said what we knew, which is we
10 don't know what this means.
11 That's an idea of some of the things that
12 we're seeing. I can tell you that we generally
13 have not favored some of the arguments about any
14 statistical difference is meaningful. From a
15 societal perspective, some people will say any
16 reduction is useful. I'm not sure that we're ready
17 to make decisions on a small reduction in opioid
18 use for a product that really doesn't show any
19 particular benefit to the patient that we can
20 identify on a societal perspective. It's asking
21 the patient to bear a lot of the burden because
22 we're now adding another drug, and none of these

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1 are side-effect free.
2 So these are debates that are ongoing,
3 discussions that are ongoing. And as I mentioned,
4 we tried to capture some of this in guidance form,
5 and I'm sure it is going to be amended based on
6 input. When it posts, I'll try and get the link so
7 that it can be sent out and you don't have to look
8 around for it. And also, if you do want to provide
9 us with some comments, it would be appreciated.
10 (Applause.)
11 DR. KROENKE: Actually, Sharon, let's see if
12 there are some questions because you ended early,
13 and we'll see if there are. You decided not to
14 answer questions, but maybe the group will ask
15 questions --
16 DR. HERTZ: So you should never end
17 early --
18 DR. KROENKE: -- that force you to answer
19 questions.
20 DR. HERTZ: -- is the lesson, so I will
21 speak longer next time
22 (Laughter.)

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1 DR. KROENKE: That's why I'm keeping you at
2 the microphone.
3 Any questions from a regulatory FDA
4 standpoint or anything Sharon said?
5 DR. HERTZ: Nat, what is the question that
6 you have?
7 DR. KATZ: If somebody did present you data
8 that said the patients on study drug used this
9 amount of opioid and the patient on placebo use
10 that amount of opioid, and there was a difference,
11 whatever their magnitude was and whatever the
12 p-value was, how would you decide whether that
13 difference was clinically important or not?
14 DR. HERTZ: Well, we're trying to have
15 conversations early in development to ask people to
16 provide some basis for us to make that decision
17 ahead of time so that, A, the sponsor knows that's
18 going to be the question; and B, we have something
19 to go with that difference. So it depends how the
20 sponsor has chosen to do that study and support why
21 they think perhaps that is clinically meaningful.
22 DR. GAN: TJ Gan from Stony Brook.

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1 Sharon, I enjoyed your talk. I have a
2 question that relates to clinical practice versus
3 trial for regulatory purposes. There is no
4 conflict between trying to take care of a patient
5 in as best we can manner versus trying to have a
6 new drug approved because I think those two are in
7 conflict in that if you want to provide the best
8 care for a patient, we know that multimodal works
9 well, and we're trying to use that model to take
10 care of patients. At the same time, we know that
11 if you use that model, it's very difficult to
12 assess what is the effect of a particular drug.
13 Again, I don't have an answer. I don't know
14 whether -- how do you go about reconciling between
15 clinical standard of care versus trying to get a
16 drug approved, understanding there's a hurdle to
17 trying to demonstrate something if you are using
18 more closely the clinical trial in a
19 standard-of-care manner?
20 DR. HERTZ: That's a really good question,
21 and there's a lot that could be said about that.
22 Let's see. You're exactly right that the use of a

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1 product in practice is often not the same as the
2 use of the product in a clinical trial that was
3 intended to demonstrate efficacy and safety for the
4 purpose of a regulatory decision. There are a
5 couple of reasons why that is, that I know about,
6 and I'm sure there are other reasons out there as
7 well.
8 We need to understand that the drug does
9 what the sponsor says it does. If it's an
10 analgesic, it needs to lower pain intensity, and it
11 should do so without dramatically worsening
12 function and global, so we often look at those.
13 Does an analgesic have to improve function?
14 That's a question. Does it have to do something
15 other than lessen pain and not have side effects
16 that are so severe to make that benefit unbalanced,
17 an unfavorable balance there. I'm going to look at
18 the transcript for this and squirm over these
19 answers.
20 So let's assume the adverse event profile is
21 not particularly bad for an analgesic, and it
22 lessens pain, and it doesn't seem to worsen other

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1 aspects. It could meet the regulatory standard.
2 Is that the best way to use the drug? Probably not
3 if it's an analgesic. So could it be studied in a
4 more clinically relevant setting? Now, I didn't
5 say should; I said could. Should is for you guys
6 to think about. Could is what I think about. And
7 the answer is sure, it can, but it's harder.
8 Right?
9 So one could develop or adopt a standard
10 multimodal
11 protocol that's been used successfully in an
12 institution and use the study drug -- use all that
13 as stable background, and then have the study drug
14 be the variable.
15 So if the multimodal approach is to take
16 somebody following -- let's say it's a big surgical
17 procedure like a knee. There's going to be a lot
18 of things done. They're going to get a block.
19 They're going to get maybe -- I don't know. Some
20 places are routinely using gabapentinoid pre-op,
21 perioperatively. Some may or may not believe in
22 NSAIDs in that setting depending on your thoughts

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1 about Cox-2 and healing.
2 So there's all that going on. And then
3 there's going to be an opioid because if you want
4 the patient to come back and let you do their hip,
5 you're going to have to give them some opioid for
6 their knee. Right?
7 So let's say you now have drug C. What
8 class is it? Is it to replace one of the existing
9 parts of that multimodal therapy so you can use
10 that as your variable? Is it an addition to that
11 to reduce the need for some of these others that
12 have adverse events, so then that's your variable?
13 So you can have a placebo-controlled study
14 with a background of this other therapy.
15 Unfortunately, if you manage your patient's pain
16 very effectively perioperatively by using a
17 standard multimodal approach that works, your assay
18 sensitivity goes away down, and you need a much
19 bigger study. Well, I'm in favor of that because
20 then I know how the product works in a much more
21 real-world setting. And we're all about real world
22 these days and real-world evidence, and that would

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1 be terrific.

2 Now, if you guys could convince the

3 companies that you consult for to do that, great.

4 But is that really the way to get new products,

5 especially potentially better products to market,

6 to burden them with a requirement that potentially

7 means more money, bigger studies, harder evidence,

8 you know, burden? I'm not sure that we're doing

9 anyone a favor, but you could argue that we're not

10 doing anyone a favor by not requiring it, so I

11 don't know. But that's sort of the reality of

12 where we are.

13 I think that another option could be to have

14 the more limited study premarketing, get your

15 product on the market, and then start really

16 looking for some big claims. Look at how fabulous

17 we are in this setting of multimodal, much better

18 than this other product, and then you can get some

19 postmarketing studies, and that would be great. We

20 just don't tend to see those.

21 So there are many ways to look at that, but

22 it's hard for me to, -- I think that there are many

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1 ways to approach this. So the bottom line

2 is -- and of course we're talking about acute pain

3 right now, but it holds true for other

4 settings -- should have chronic pain drug be

5 studied in the absence of all the things we don't

6 allow people to do typically in clinical study?

7 So if we're lucky, the anticonvulsant or

8 antiepileptic that's been stable for 3 months is

9 allowed to continue, and maybe sometimes physical

10 therapy or some other complementary therapy, if

11 it's stable, is allowed to continue. But

12 typically, those are not parts of the clinical

13 study.

14 So the chronic pain drug may also be studied

15 in a more narrow manner than ideal chronic pain

16 management would prefer. But then it's up to you

17 folks to integrate it into that, assuming you ever

18 get coverage from your patients' insurers for any

19 of that. That's a whole another story.

20 Did I use up my time?

21 DR. KROENKE: No, no. That's good.

22 DR. HERTZ: No more questions. Okay.

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1 DR. KROENKE: There may be more questions at

2 lunch [inaudible - off mic].

3 Excellent. Our final presentation before

4 lunch will be by Carlos Pena, who's the director at

5 the Division of Neurologic and Physical Medicine

6 Devices, Office of Device Evaluation at the FDA in

7 Silver Spring as well; and he'll be talking about

8 opiate-sparing clinical trials and objectives

9 related to devices.

10 Presentation - Carlos Pena

11 DR. PENA: Good morning. I always get

12 nervous when FDA's before a lunch session. The FDA

13 barring people from getting food is not the

14 branding that I was hoping we would go out with.

15 Devices are an up and coming technology

16 sector that I think it's worthwhile to spend a

17 little bit of time with you on, introducing you to

18 medical device regulation, and specifically three

19 parts of this presentation, including introducing

20 you to that regulation. The second part is some

21 factors to consider in what we look for in

22 evaluating devices, and the third is the best ways

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1 to engage. I'm not familiar with a lot of you, and

2 I'm hoping that we can change that.

3 So our vision at Center for Devices and

4 Radiological Health is that patients in the U.S.

5 have access to high-quality safe and effective

6 medical devices. Public health importance is first

7 in the world, and we take that pretty seriously.

8 I'm going to show you some data that speaks to

9 supporting that vision, and our primary interest is

10 getting products to patients.

11 First off, what is a medical device? A

12 medical device is defined as an instrument,

13 apparatus, implements, and it goes on and on and

14 on. So you might be saying, Carlos, there are

15 several provisos, some addendums, a couple

16 clarifications; what is a medical device? If a

17 diagnosis treats or prevents a disease in a manner

18 other than through chemical action, it may be a

19 medical device. And one can classify a device as a

20 medical device, even in the absence of claims, when

21 it impacts the structure of function of the human

22 body.

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1 We classify our devices into three
2 classifications, class 1, 2, and 3, with regulatory
3 oversight increasing from class 1 to class 3. And
4 the device classification regulation defines the
5 requirements for any given device. For example,
6 most class 1 devices are exempt from submitting an
7 application to FDA; most class 2 devices are what's
8 called premarket notification or 510(k); and most
9 class 3 devices require premarket approval.
10 They're PMAs, and we provide oversight across these
11 three classes using tools known as general and
12 special controls, which help to communicate to the
13 sponsors what they need to do to get their product
14 to market.
15 As mentioned on the last line, medical
16 devices can be classified into three
17 classifications, two of which are highlighted here,
18 class 3 and class 2. These are the higher risk
19 classifications. For example, we receive several
20 dozen PMAs or class 3 devices each year. These are
21 the highest risks and require clinical data,
22 typically.

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1 A second pathway is a 510(k) submission
2 pathway, so there's something already on the market
3 for which these products compare themselves to. We
4 receive several thousand 510(k)s each year. They
5 may contain clinical data, but typically they do
6 not. And finally, a third regulatory pathway is
7 the de novo submission process, which includes
8 devices that aren't comparable to anything on the
9 market and present a lower risk than other types of
10 devices. Once they have been granted to enter the
11 marketplace, they then serve as a predicate to
12 subsequent devices that move along the 510(k)
13 pathway, class 2.
14 So when is clinical data needed? And this
15 often comes up in the device realm. Typically for
16 PMAs, clinical data is needed. For de novo
17 submissions, clinical data may be needed but may
18 not always be needed. And 510(k) submissions,
19 clinical data is typically not needed, although
20 there are cases where clinical data was submitted.
21 So you're again saying, Carlos, okay,
22 there's a lot of provisos here, addendums. When

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1 and how do we find out if clinical data is really
2 needed for our submissions? And my response to you
3 is that you can request feedback through the
4 presubmission process through our center before
5 hopefully starting your study. And I'm going to
6 return to that about how to engage the Center for
7 Devices. The presubmission process is a free
8 process, and hopefully people use that process to
9 engage us before they begin studies, which can be
10 expensive.
11 Here's a favorite slide of mine. We've been
12 engaged in the neurotechnology sector for some
13 time. Here I show you an array of products
14 beginning with neurothrombectomy devices on the
15 left-hand side, epilepsy, and ADHD diagnostic,
16 prosthetic arm, migraine, device, and
17 microcatheters for the neurovasculature. The goal
18 is not to discuss individual data sets with you for
19 each device, but share with you here that each
20 device went through a regulatory pathway that was,
21 in part, tailored to the individual risks and
22 benefit profile of the device. And when other

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1 products are targeted that may involve different
2 product areas across the agency, we work with our
3 colleagues, such as Sharon and her staff, to
4 coordinate our reviews.
5 First I'd like to share with you how serious
6 you are about standing up clinical studies that
7 evaluate devices. The faster you can stand them
8 up, the faster you can evaluate the data. And the
9 faster you can come out with the data, the faster
10 you can submit an application to us.
11 Here I show you decreasing timelines over
12 the past several years where in FY11, it took
13 approximately 400-plus days to reach a full
14 approval of an IDE study. IDE is investigational
15 device exemption, a clinical study that we use to
16 evaluate medical devices. FY13, we dropped that by
17 half, and '14, '15, '16, and '17 is late data.
18 That is now down to 30 days, the median time to
19 full approval.
20 That's a pretty striking drop. We take
21 safety very seriously, but we would like to start
22 these studies as quickly as possible with safety

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

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

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

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

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

9 I attended conferences actually yesterday on
10 the west coast. I was in the meeting and walking
11 down the exhibitor booths, and someone comes up and
12 says, "Hey. Can you approve this device?"
13 (Laughter.)
14 DR. PENA: And I'm looking at that list, and
15 the questions that we need to ask in the device
16 realm, which are comparable in the drug realm, is
17 that there are a lot of factors that we need to
18 take into consideration. And we weigh all of these
19 factors almost in a tailor-made approach. So it's
20 never an easy question, but I am assured that the
21 device questions that we do ask help to get the
22 right products to the marketplace.

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

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

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

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

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

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

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

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

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

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

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

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

11 If people think it's too early to contact
12 us, that's probably the best time to contact us,
13 because it can be very expensive. It would be a
14 missed opportunity if you are involved in device
15 development. You do your study. You have all the
16 results packaged up and ready to go, and we're not
17 on the same page with regard to the outcomes, or
18 the results, or the methodology that was used.

19 There's a lot of information available, recent
20 article in Neuron. We also have a website for the
21 neuro and physical medicine devices division. And
22 we have had a number of webinars online that map

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1 out the different regulatory pathways for products
2 in this area.

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

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

22 I'm also accompanied by two individuals from

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1 the Center for Devices, Dr. Jonathan Jarow and
 2 Dr. Allen Chiu. We're sort of all along the back
 3 wall there, evaluating all of you and the questions
 4 there. But if you get a chance, it would be great
 5 to make some contacts. I think we want to have a
 6 good start to this technology piece of the puzzle
 7 and make sure that it is successful.
 8 Just in case, if you haven't taken anything
 9 away from my talk -- and if you're focusing on dry
 10 cleaning or what you're doing at lunch time -- I'm
 11 giving you my contact information. Sometimes I
 12 hear a lot of you, I don't know who to contact at
 13 FDA. Where do I start with devices? There's my
 14 email address. I think you'll be surprised about
 15 the contact that we have and the interaction we can
 16 have with device development. Thank you.
 17 (Applause.)
 18 DR. KROENKE: We have about five minutes
 19 before we close. Question? Yes?
 20 DR. FARRAR: A very interesting talk. One
 21 of the questions that always comes up, if we take a
 22 potentially opioid-sparing process, like a spinal

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1 cord stimulator perhaps or nerve stimulator, there
 2 are spinal cord stimulators that you can put in
 3 temporarily and remove, and they're ones
 4 that -- sorry. John Farrar, University of
 5 Pennsylvania. I forgot about the recording. And
 6 there are spinal cord stimulators that require an
 7 open procedure to do.
 8 So I come to you with a new device, where
 9 I'm going to plaster your entire spine. I'm going
 10 to just open you up and put something from guzzled
 11 to zatch. And I show you that it's as safe as
 12 anything else. I guess what I'm getting at is how
 13 is the decision made not only about the device in
 14 terms of its functioning and so on, but ultimately
 15 the risk of insertion, or the risk of use, and then
 16 ultimately the potential benefit relative to other
 17 devices that work in the same space?
 18 I understand that's a very complicated
 19 issue, but I just wondered what --
 20 DR. PENA: That's the questioning of the
 21 conference all the time. There are a lot of points
 22 there to unravel. One is the invasiveness of the

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1 product. One is how do you assess the benefit?
 2 What is the benefit, purported benefit? One is
 3 where is the patient at in the continuum of
 4 treatment? One is where do we have prior evidence
 5 of the product and what is the prior clinical
 6 studies available? How are benefits characterized
 7 and by what measures? Are these clinicians or
 8 patients?
 9 If you have a data set, how robust that data
 10 set is? Is there some uncertainty in that or not?
 11 And is there a least burdensome way, if there is a
 12 robust effect, of getting that to the marketplace?
 13 How should we work together to really expedite that
 14 least burdensome to the marketplace?
 15 Those are all the types of things that we
 16 would walk through and try to look at the totality
 17 of the evidence in making a decision. If those are
 18 all in place, there's a high degree of benefits,
 19 there's a low degree of uncertainty, there's a low
 20 degree of risk or the risk has been mitigated
 21 through labeling or other experience, when those
 22 things line up and we've talked about that in a

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1 presubmission before you've done a study, we're in
 2 a good place I think.
 3 When those things have not been discussed
 4 and we have uncertainty about the beneficial impact
 5 of those that have been treated versus the control
 6 group that have gotten standard of care that are
 7 doing probably maybe better, when those
 8 uncertainties start to add up, that sort of shifts
 9 the ratio of the benefit-risk, the decision process
 10 that we make in devices.
 11 So I don't really have a yes or no answer
 12 would we go forward with that. I have the factors
 13 that we would need to think through, that my
 14 clinicians, that my scientists, that my engineers
 15 would need to walk through in a review team to make
 16 the best decision of whether to stand that study up
 17 in an IDE study or to make a decision of getting
 18 that to the marketplace. It's a great question.
 19 DR. KROENKE: A question there?
 20 DR. FIELDS: Howard Fields, UC San
 21 Francisco. How good was your postmarketing
 22 follow-up for devices? Are there requirements to

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1 keep patient records? How would that be done?
 2 DR. PENA: Right. For premarket studies, we
 3 may require 12 months of safety and effectiveness
 4 data, depending upon the invasiveness of a device,
 5 during the clinical phase of product development
 6 before that is marketed. That will give us a piece
 7 of the puzzle about what we can expect long term.
 8 Then there's also postmarket surveillance
 9 that we have. Office of Surveillance and
 10 Biometrics looks at safety signals. We don't know
 11 the denominator, but they review reports of these
 12 signals that may come in through our databases,
 13 through voluntary reports about different products.
 14 That's another method, that we are evaluating
 15 different products in the marketplace.
 16 In some cases, when you talk about class 3
 17 devices, like I mentioned at the beginning of the
 18 talk, there may also be post-approval study
 19 requirements or post-approval studies that need to
 20 be performed over more than one year, 3 years,
 21 5 years. That depends, again, upon these types of
 22 factors that we need to walk through at the time of

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

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

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

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1 I'm getting at, is the confusion from the patients
 2 or the physicians' perspective of what evidence was
 3 used for the FDA to make that 510(k) clearance
 4 designation so that they don't know what to
 5 communicate either to the patients or for the
 6 patients to understand what they're using.
 7 DR. PENA: So let me just answer that, and
 8 maybe Jonathan Jarow would like to take a swing at
 9 this too. But the 510(k) decisions include a
 10 summary of safety and effectiveness. In that
 11 summary there is information about what the
 12 evidence that was included in that submission came
 13 with that application. That as a safety would be a
 14 good source for information for physicians to
 15 convey to the patients if that's a need.
 16 Jonathan, do you want to do anything
 17 further?
 18 DR. JAROW: It's not an exact analogy, but
 19 the 510(k) process could be compared to generic
 20 drugs. And when we approve generic drugs for
 21 marketing, we do not require clinical evidence that
 22 these drugs are safe and effective for their

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1 intended use. We require that they show
 2 bioequivalence to a reference-listed drug.
 3 This process is very much similar to that.
 4 So if there is a predicate device that's marketed,
 5 that's been found to have reasonable assurance of
 6 safety and effectiveness, and this device has been
 7 shown with bench testing and other testing to be
 8 within all the same parameters, so very much like
 9 bioequivalence, you can get to market without any
 10 clinical data whatsoever.
 11 However, if they're outside of those
 12 parameters in any way, shape, or form, it may be in
 13 order to demonstrate substantial equivalence that
 14 clinical data are required.
 15 DR. PENA: Right.
 16 DR. JAROW: So some of the special controls
 17 for class 2 devices actually require clinical
 18 data --
 19 DR. PENA: Exactly.
 20 DR. JAROW: -- with each new device.
 21 DR. PENA: A good example is
 22 neurothrombectomy devices. Those require clinical

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1 studies as part of their clearance in the 510(k)
 2 paradigm.
 3 DR. KROENKE: Thank you.
 4 (Applause.)
 5 DR. KROENKE: What's really good is nobody
 6 fell asleep before lunch, but we're getting more
 7 feisty. So that's a good sign for our discussion.
 8 (Laughter.)
 9 DR. KROENKE: There are a lot of hands that
 10 went up during the morning presentations. I hope
 11 you've remembered your question, and your memory's
 12 not dulled by feeding yourselves.
 13 I think what we said is we're going to have
 14 lunch and then rejoin here, do you think a 12:15 or
 15 12:30?
 16 So 12:15, whoever's here, we're going to
 17 start discussing. If you're not quite finished,
 18 you can bring your lunch to this room, but you'll
 19 have nearly 45 minutes to lunch next-door. We'll
 20 rejoin here at 12:15. Thanks.
 21 I do want all the panelists at that time to
 22 come up to the table for lunch, so everybody who

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1 spoke this morning needs to be at the table at
 2 12:15.
 3 (Whereupon, at 11:35 a.m., a lunch recess
 4 was taken.)
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1 AFTERNOON SESSION
 2 (12:20 p.m.)
 3 DR. KROENKE: As we get started here, we're
 4 going to have a couple minutes, up to 3 to 5
 5 minutes, for updates from Michael Oshinsky from NIH
 6 and Jeremy. Everybody has been hearing about
 7 this -- I'll use the short term, the "pain
 8 moonshot," -- well, they did it for cancer, so this
 9 is important; so this extra money over the next
 10 several years, targeted to the kinds of things that
 11 people are interested in.
 12 Michael?
 13 Presentation - Michael Oshinsky
 14 DR. OSHINSKY: Thank you very much. We're
 15 going to be really short, Jeremy and I. I just
 16 wanted to introduce the programs and the planning
 17 that we're at, at this stage, for the HEAL
 18 Initiative, which is helping to end addiction long
 19 term.
 20 My name is Michael Oshinsky. I'm the
 21 program director for pain and migraine at the
 22 NINDS, which is one of the institutes at NIH.

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

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

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

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1 this in the most fiscally responsible way and in
 2 the way that's really going to get the most benefit
 3 to the patients out there.
 4 So that's one of the hats I wear. I will
 5 just also mention -- and it's important in this
 6 audience -- I'm an emergency physician by training.
 7 In fact, I spent 15 years at George Washington
 8 University just down the road from here. And if
 9 any of you decide to go on a segway tour this
 10 afternoon and fall of your segways, and come up
 11 with a Colles fracture at GW, which was a pretty
 12 standard thing that we would treat this time of the
 13 year, I would have been a face that you would have
 14 seen happily injecting you with some IV dilaudid to
 15 help treat your pain while we set your Colles
 16 fracture.
 17 (Laughter.)
 18 DR. J. BROWN: So I'm interested in the
 19 opioid space as well. NINDS is not in that space
 20 directly. That is really the mission of NIDA, the
 21 National Institute on Drug Abuse. But the opioid
 22 space is an equal space, is an equal target, if you

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1 like, for this helping to end addiction long term.
 2 And there will be many programs in that space, in
 3 the opioid addiction space, including medically
 4 assisted therapy, looking at the best ways for
 5 doing that. Much of that, of course, happens in
 6 the emergency department setting, but much of it
 7 happens elsewhere in clinics that many of you may
 8 run.
 9 So there are those two sides of it. We're
 10 happy to take a few very, very limited questions
 11 right now because we don't want to take away from,
 12 really, what the main focus is. I'll be here
 13 tomorrow to answer any more questions. We're both
 14 very easy to find online. Jeremy.Brown@nih.gov is
 15 my email. I'm happy to answer any questions that
 16 come up or just shoot me an email. Thank you.
 17 DR. KROENKE: Maybe we can take a couple of
 18 questions. My guess is there are either no
 19 questions or there are many questions. But if
 20 there are a couple of questions, we'll be happy to
 21 entertain, and then we'll move on.
 22 Any questions at all? Yes?

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1 DR. HAYTHORNTHTWAITE: Can you tell us what
 2 the timeline is for the Clinical Trials Network
 3 RFA? Sorry. That was Jennifer Haythornthwaite.
 4 DR. KROENKE: Since I said, everybody who's
 5 going to speak today will turn the microphone on
 6 and say who you are and where you're from. That's
 7 for the transcriptionist. So start over.
 8 DR. HAYTHORNTHTWAITE: That was Jennifer
 9 Haythornthwaite at Johns Hopkins University, and
 10 the question was about when the RFA is coming out
 11 for the Clinical Trials Network.
 12 DR. J. BROWN: Thank you. So there is
 13 indeed a notice of intent to publish, which means
 14 that we're thinking about putting an RFA out.
 15 Actually, I can tell you that at least 4 RFAs have
 16 been written. I know because I wrote them. And
 17 they have gone through various stages of vetting
 18 and review, and they are currently waiting for NIH
 19 leadership, and then ultimately the HHS leadership,
 20 to approve these and make sure that they fit with
 21 the overall strategic plan and mission of the HEAL
 22 Initiative, and then we'll put them out.

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1 We've had various target dates that we have
 2 tried to meet, and for one reason or another, we
 3 didn't meet them. And we know this is frustrating
 4 to you. And more importantly, every month that
 5 we're waiting, 62,000 people a year, you divide
 6 that by 12; how many is that a month, right? And
 7 then you think if we could move the needle by
 8 3 percent, that's a lot of people who are dying
 9 every month because we haven't started some of
 10 these programs yet.
 11 So we're aware of it, and as soon as we can
 12 get them out. But they're written and ready to go.
 13 DR. DWORKIN: I'm Bob Dworkin. I'll ask a
 14 follow-up question to Jennifer's. Is it correct to
 15 assume that given the delay in posting the RFAs,
 16 that the submission date that's now online of
 17 September will be moved forward?
 18 (Laughter.)
 19 DR. J. BROWN: Thank you for pointing that
 20 out. I should have gone back and corrected that.
 21 You're absolutely right. Just so that you know,
 22 our initial plan was to get this money out in FY18.

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1 FY18 ends at the end of September. So that was a
 2 very ambitious date. We knew we couldn't meet it,
 3 but then we wanted to get this money out in
 4 calendar year 18 ending in December. That was also
 5 a very ambitious date. We realize that those dates
 6 are now not -- we're not going to reach them, but
 7 we really are working very, very diligently.
 8 Yes, I know I'm from the government and I'm
 9 telling you that we're working diligently.
 10 (Laughter.)
 11 DR. J. BROWN: But we really are, and we're
 12 just waiting for people with more wisdom than us to
 13 give us the approval. But that does need to be
 14 corrected. Thank you.
 15 Working Lunch and Group Discussion
 16 DR. KROENKE: Jeremy said at least he'll be
 17 around, and Michael maybe. But they'll be around
 18 yet during this meeting, so please curbside them if
 19 desired. And we also have long discussions
 20 tomorrow; it may come up. I really appreciate
 21 their attendance because this will be a very
 22 important source of funding for this area we're all

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1 interested in.
 2 So having said that, it's going to be now
 3 open for an hour for discussion and questions.
 4 Believe me, if nobody has any questions, a few of
 5 the people here do have questions, but I'd rather
 6 start with questions from the audience. I know
 7 there's at least 10 hands that went up this morning
 8 that I wasn't able to recognize, so let's start.
 9 And since I don't know people's names, I'm going to
 10 do a lot of pointing. So again, turn the mic on,
 11 say your name, and ask your question.
 12 DR. GROL-PROKOPCZYK: I'm Hanna
 13 Grol-Prokopczyk at the University of Buffalo. So a
 14 lot of the morning talks were about defining opioid
 15 sparing, and I really liked Nat's talk for trying
 16 to get very concrete about that and also about
 17 defining or conceptualizing some other things like
 18 opioid related adverse events.
 19 This is maybe a terminological critique, but
 20 hopefully one not so petty as talking about commas
 21 and hyphens. Nat, your definition of opioid
 22 sparing seemed to essentially be reduction of

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1 opioid related adverse events. And it seems to me
 2 that that's sort of analogous to calling something
 3 a weight loss drug when it doesn't cause weight
 4 loss, but it simply reduces the negative effects of
 5 excess weight. So I just wonder if there are sort
 6 of two different things, there's reduction of
 7 opioids and there's reduction of the negative
 8 consequences of opioids, and maybe those deserve
 9 different terms to describe them.
 10 Then a second question having to do with
 11 conceptualizations or definitions was whether it's
 12 worth discussing what we mean by maintaining pain
 13 control because you kept saying that it goes
 14 without saying that we want to reduce these adverse
 15 outcomes while maintaining pain control. And as
 16 TJ's talk showed graphically, patients may be very
 17 willing to make these cost benefit analyses where
 18 they're willing to give up a certain amount of pain
 19 reduction in exchange for reduction in those side
 20 effects.
 21 So what do we mean by maintaining pain
 22 control? What if the side effects go way down and

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1 the pain control gets a little bit worse? But what
 2 if that's still something that patients would
 3 prefer? Is that then disqualified as a successful
 4 example is of opioid sparing?
 5 DR. KROENKE: And just to comment -- because
 6 this will frame, and I think you did that. So the
 7 degree to which people have a question, they may
 8 initially target to some member of the panel,
 9 that's a good thing because otherwise, panels are
 10 going to look at each other quizzically and say
 11 who's going to answer that, and then sometimes
 12 every panel will have that person. And if the
 13 other panelists have a further comment about it
 14 that's contributing, fine, but we'll try to make
 15 sure every question doesn't have every panelist's
 16 comment on it.
 17 But that's a very rich question, so, Nat, I
 18 presume you want to start because she mentioned you
 19 by name.
 20 DR. KATZ: She did do that. In terms of the
 21 first suggestion, should we draw a conceptual
 22 distinction between the amount of opioids consumed

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1 and the consequences to the patient of a change in
 2 the amount of opioids that they've consumed, and
 3 presumably at this meeting a reduction because
 4 we're talking about reduction, I kind of like that
 5 idea, honestly. And maybe it would be clarifying
 6 to try to not combine them into the same concept
 7 but make them into different concepts.
 8 I think Sharon already alluded to a way of
 9 thinking where first you figure out if the
 10 consumption went down or not. And then once you've
 11 done that, you ask the next question, which is,
 12 well, did that actually matter to the patient or
 13 can we even know whether it mattered to the
 14 patient.
 15 So I kind of like that. It probably
 16 shouldn't be too hard to figure out words for these
 17 things, right? Amount of opioid consumed and the
 18 clinical consequences of that, something like that.
 19 I like that.
 20 The second one was about these kind of -- I
 21 don't want to call them ambiguous, but the
 22 interpretation of composites, where you're trying

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1 to see, gee, your pain went up by some amount but
 2 your side effects went down by some amount. How do
 3 we determine whether you're better overall, and
 4 would we have tolerance for those kind of more
 5 difficult to interpret scenarios.
 6 So if your opioid consumption goes down and
 7 your pain is better, and your opioid side effects
 8 are improved, then that's unambiguous. I know that
 9 you're better. If your side effects go down and
 10 your pain goes up, now I've got work to do to
 11 figure out if you're better, or worse, or the same.
 12 So conceptually, I like what you're saying,
 13 that there are actually combinations where somebody
 14 could be overall better off even though their pain
 15 is a little worse or vice versa. So from a
 16 clinical perspective, when you see patients, you
 17 know that that's true from a clinical -- I'm always
 18 thinking about, well, how do you demonstrate it in
 19 a clinical trial?
 20 In terms of demonstrating that in a clinical
 21 trial, boy, that is very hard work. You'd have to
 22 do a lot to -- it might sound easy. It's not easy

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1 because having published several papers on trying
 2 to come up with methods of computing and validating
 3 composite response indices, including ones just
 4 require looking at benefit or the ones where you're
 5 actually combining safety and efficacy, it's
 6 actually hard work. But conceptually, I'm totally
 7 on board.
 8 DR. GROL-PROKOPCZYK: Jen said something
 9 earlier about -- what are they called? Door
 10 procedures? I guess there are things that could be
 11 discussed for how you would operationalize that.
 12 DR. HERTZ: I guess my question
 13 is -- because remember, I'm not answering anything
 14 today. I'm just going to ask more questions.
 15 MALE VOICE: Is your name Sharon Hertz?
 16 DR. HERTZ: The new Sharon.
 17 DR. KROENKE: Sharon Hertz from FDA.
 18 DR. HERTZ: Oh, thank you.
 19 MALE VOICE: And it's not a question.
 20 (Laughter.)
 21 DR. HERTZ: Janet knows me.
 22 Why would you enroll somebody in a clinical

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1 study, separate from practice, at a level of pain
 2 management, and a level of analgesic, and a level
 3 of analgesic adverse events that hasn't already
 4 been optimized? So if somebody is willing to give
 5 up some analgesic effect to lessen side effects,
 6 shouldn't that be the baseline in which they go
 7 into the study? Because otherwise, it's a
 8 confound. The sparing effect is now confounded
 9 with the fact that they didn't need so much opioid.
 10 So I think it's a bad place to start a
 11 clinical study because is the benefit attributable
 12 to the drug or just to less opioid, and you could
 13 have achieved that without the drug. So it becomes
 14 very challenging if that's how you start. The
 15 baseline has to be a little cleaner, I think, in
 16 order to separate out the effect of the drug versus
 17 the effect of simply reducing opioids.
 18 DR. KROENKE: I'll just make a comment; I
 19 think a couple, which was mentioned, this morning.
 20 And I'm not going to talk about the perfect trial
 21 that goes to the FDA. I'm going to talk about a
 22 clinical thing. But one thing that was raised this

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1 morning and it keeps coming back is pain benefit
 2 versus adverse effects of the pain treatment. Even
 3 if we make each of those composite measures, like a
 4 composite bad scale, like these are all the bad
 5 things that can happen and here's your total score,
 6 which is probably more useful than a individual
 7 adverse symptom checklist, it also has a value of
 8 one outcome in trials rather than 12 in multiple
 9 hypothesis testing. It has to be relevant, though.
 10 I also think it's intriguing to come up with
 11 a question that balances it. And this is not
 12 psychometric; I'm just making it up on the fly.
 13 But wouldn't it be a wonderful world to ask a
 14 single question, during and at the end of the
 15 trial, given your current level of pain and any
 16 side effects you might have had from the treatment,
 17 what's the likelihood you would want to continue
 18 this treatment? And you could ask that. Again,
 19 I'm making this up.
 20 But I do think of this concept, why don't we
 21 incorporate the patient into an assessment of pros
 22 and cons, at least the secondary outcome?

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1 DR. KATZ: Yes, that has been done. Some of
 2 you may remember Janssen funded the development of
 3 an instrument called the PADT. I forget what it
 4 stands for, but it was designed to evaluate
 5 opioid -- it was designed to be a measure
 6 clinicians could use in practice when they're
 7 assessing the benefits and harms of opioid therapy,
 8 and they're real patients.
 9 We asked about benefits, and we asked about
 10 harms, and then at the end, there was an item
 11 exactly like that, considering all the benefits, do
 12 you think that they outweigh any side effects
 13 you're having or something like that. So that
 14 instrument exists and data was collected with that,
 15 but we never actually looked at the performance of
 16 that particular instrument. That could be done
 17 with available data, I think.
 18 DR. KROENKE: A lot of other questions. Way
 19 in the back, gentlemen? Yes?
 20 DR. SIMON: Simon from Boston. In that
 21 context, I was wondering of the instruments that
 22 were presented this morning -- we saw some for

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1 acute pain and some alluded to chronic pain -- how
 2 many of those instruments were actually developed
 3 with patient involvement in each of the questions
 4 determining the utility of the question, the
 5 understanding of the question, and the impact of
 6 the clinical relevance to the patient?
 7 Was this done with patients or was this done
 8 in the context of what we think that we know better
 9 what a patient really cares about?
 10 DR. KATZ: I can answer that with respect to
 11 the instrument that I showed, which was developed
 12 for acute pain, and then, TJ, it would be good to
 13 hear you answer the same question with respect to
 14 the instruments you presented.
 15 In the one that we presented, it was a
 16 soup-to-nuts, right out-of-the-box scale
 17 development program, so patients were involved
 18 every step of the way. There were I think maybe
 19 something like 300 patients involved by the time we
 20 were done, a multiplicity of different kinds of
 21 surgeries balanced with respect to gender and age
 22 and all the things that you would expect; bias

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1 carefully looked at, at the end, to make sure the
 2 different subgroups didn't respond differently and
 3 patients are involved in every step of the way in
 4 terms of item evaluation, item reduction, all that
 5 kind of thing.
 6 So in that particular instrument, yes, but
 7 that was only validated for acute pain.
 8 TJ?
 9 DR. GAN: So I presented a few. One of them
 10 is the opioid related symptom distress score, the
 11 SDS, which I mentioned earlier was initially
 12 developed by Russ Portenoy for chronic pain. And
 13 we changed it a little bit to suit more in the
 14 acute setting and specifically trying to address
 15 the opiate related adverse events. And again, it
 16 was part of the multicenter studies where about 300
 17 something patients that we initially tested in one
 18 population and validated in another population,
 19 looking at inter-variable correlations between the
 20 validated group and the initial group.
 21 So it's validated in that sense. And as I
 22 showed you the data, there was a correlation

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

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

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

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

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

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

22 We will never have a meeting on gabapentin

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

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

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

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

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

11 MALE VOICE: [Inaudible - off mic].

12 DR. DWORKIN: Or TJ?

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

15 DR. DWORKIN: Sharon is fine.

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

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

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1 in-house thing. And then committee members said,
 2 "Why does any of that matter if they still go home
 3 on an opioid?" with the idea being, potentially,
 4 you're not going to get away with replacing
 5 somebody's knee without some opioids, but really
 6 the opioid-sparing benefit would be something other
 7 than that interoperative period. But perhaps
 8 really preventing the need for opioids as an
 9 outpatient, and therefore reducing the amount of
 10 opioid available in the community if there's
 11 leftover and so on.
 12 DR. KROENKE: We'll finish this. Yes? TJ
 13 and then Nat.
 14 DR. GAN: Interesting observation. And
 15 imagine yourself, Bob -- god forbid that you don't
 16 need surgery. Let's say imagine you needed a
 17 surgery. You're now in the post-op period lying in
 18 your bed. You are nauseous, 10 out of 10. You are
 19 throwing up. You are constipated or you haven't
 20 opened your bowels for the last 3 days. You cannot
 21 pee, and someone's going to come in with a catheter
 22 to put into your bladder. You are delirious.

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1 You like to be in that state?
 2 (Laughter.)
 3 DR. GAN: No. I understand that you are
 4 talking about the major event, respiratory
 5 depression, death; I get that. But are we saying
 6 that those are actually great states for the
 7 patient to be in?
 8 DR. DWORKIN: TJ, I completely agree with
 9 you, but that's a different -- I'm going to be
 10 provocative. That's a different IMPACT meeting.
 11 That's an IMPACT meeting where Henra Kellick [ph]
 12 would be here. And we have no surgeons in the
 13 room. We need surgeons here. We need more
 14 anesthesiologists. And that would be a meeting on
 15 research designs for clinical trials of multimodal
 16 analgesia.
 17 So I completely agree with where you're
 18 coming from, but this is a meeting on opioid
 19 sparing in the context of an opioid epidemic
 20 crisis. And to me, then the key outcomes are death
 21 from overdose and substance-use disorder, OUD.
 22 DR. KROENKE: So here's what I'm going to

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1 do, then I'll let comments come back. I'll take a
 2 few from the room. Back there, you stood up, and
 3 then you. You must have been excited, in the back
 4 of the room.
 5 DR. STEINER: Yep. That's me. Deb Steiner
 6 again. Hi.
 7 I guess for me, it would be helpful
 8 to -- first of all, when I first looked at the
 9 agenda for the meeting, we're talking both about
 10 acute and chronic pain, which I found really
 11 exciting, but they're very different. And I think
 12 the outcome measures are going to be different.
 13 Also, I completely agree that the side
 14 effects -- I mean, these are all serious, they're
 15 important, but we're talking about pain and we're
 16 talking about efficacy. And I hope that we focus
 17 on that pain intensity part, too, because as much
 18 as the patients don't want nausea, vomiting, and
 19 constipation, we're administering these
 20 medications because we don't want them to be in
 21 pain.
 22 So I just think to me, a little bit, kind of

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1 stepping back at a higher level and just the
 2 broader approach would make it a little easier for
 3 me to kind of follow what kind of outcome measures.
 4 And certainly the issue with acute that's similar
 5 to chronic is the idea of even initiating opioid
 6 treatment and where that might lead. Thank you.
 7 DR. KROENKE: And you, yes?
 8 MS. COWAN: A couple of things. I'm sorry.
 9 Penny Cowan, American Chronic Pain Association.
 10 Sorry about that.
 11 One of the things I want to say is that I've
 12 heard, sometimes, patients mention -- and I guess
 13 since I'm that voice of the person living with
 14 pain -- is that there's a saying, "Nothing about us
 15 without us." And I think that starts at the bench
 16 in research. So keep that in mind, that there is
 17 nothing about us without us.
 18 But then I have to wonder, what is the
 19 motivation for pharmaceutical companies, if we're
 20 talking about opioid sparing, to say we want to
 21 make less of your drug? I mean, I can't see that's
 22 a motivation for a lot of them. But then my real

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1 question is -- and I don't know whether it's to Nat
 2 or not -- when we're looking at measuring pain,
 3 it's so subjective for everyone. Why are we
 4 looking at measuring their level of function, and
 5 why aren't we asking them what is their expectation
 6 out of this treatment, whatever it might be?
 7 I mean, there are so many components to
 8 living with pain other than just taking the
 9 medication. But we set everyone's expectation up
 10 for I'm going to give you this pill and it's gonna
 11 make you better. That's our expectation without
 12 knowing that part of that responsibility is ours,
 13 but part of it is we need other components. And I
 14 don't ever see that in trials. I would love to see
 15 a multidisciplinary pain trial done to say this is
 16 the way to do it so that payers will begin to pay
 17 for it.
 18 DR. KROENKE: What I'll do is I'll
 19 alternate, because I know John has his hand up.
 20 But I think either Sharon or Nat both had -- and
 21 this isn't linear; it might have been on a previous
 22 comment. But any comments that you have, and then

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1 I'll take a couple more from the audience.
 2 DR. HERTZ: I actually disagree a little bit
 3 with Bob, and maybe we didn't invite all the right
 4 people, but there are two aspects of this. One is
 5 when an opioid is necessary because toradol isn't
 6 enough? How do you lessen the negative effects?
 7 It's a quality of life, quality of experience, kind
 8 of issue. I see that as predominantly an acute
 9 pain issue, but no, it's also somewhat chronic or
 10 true for people with chronic pain.
 11 The second part of that is one that's really
 12 curious to me because if we're trying to replace
 13 opioids because there's a large amount prescribed
 14 and there's a large amount sitting in medicine
 15 cabinets and getting into the wrong hands, are we
 16 talking about the development of novel non-opioid
 17 analgesics, and is that actually opioid sparing?
 18 So that's my question.
 19 DR. KATZ: I guess I would agree with Bob
 20 that it would be a good idea to determine what this
 21 meeting is about relatively early in the agenda.
 22 (Laughter.)

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1 DR. KATZ: So in that sense, I agree with
 2 you, at least agree with the question. When Mao
 3 Tse Tung took over in China in 1939, 80 percent of
 4 the men in the Pearl River region of China were
 5 addicted to opium, and it was a huge societal
 6 problem. That's why they had to opium wars, which
 7 the emperors were both defeated.
 8 So what did Mao do about his opioid
 9 epidemic? He made it capital punishment to import
 10 opium. He took all the addicts and put them in
 11 sanatoria. Opioids became unavailable in China for
 12 40 years or what have you, even if you're writhing
 13 in cancer pain. And the opioid problem was gone.
 14 So if that's the type of opioid sparing that
 15 we're talking about, sure. We can have a meeting
 16 about that. None of us are probably the right
 17 people to be in the room -- and maybe Eric but
 18 nobody else --
 19 (Laughter.)
 20 DR. KATZ: -- since he's the only person who
 21 really talked about that.
 22 My experience with the IMPACT group is that

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1 we're generally talking about how to design and
 2 conduct clinical trials that inform scientific and
 3 therefore regulatory decision-making in the context
 4 of drug development. Even though we take great
 5 pains to say that it's not the case, well, it kind
 6 of is the case.
 7 So if we're going to say something useful
 8 about opioids sparing in that context, it's
 9 probably more about the design of strong,
 10 non-addictive opioids, and designing therapies that
 11 accomplish what TJ said, which is to reduce the
 12 burden of opioids. So that's why I came at it from
 13 that point of view. But if we're talking about
 14 every imaginable intervention to reduce the
 15 societal burden of the opioid problem, well, yeah,
 16 I agree that that's a rather different kind of
 17 meeting.
 18 DR. HERTZ: This is Sharon. I just have to
 19 interject so that I don't actually have to leave
 20 right now. This meeting does not have anything to
 21 do with anything for any regulatory body. This is
 22 a discussion of the current state of the science

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1 and knowledge of a number of highly experienced
 2 people in the field. And any attempt to influence
 3 regulatory decision-making should be taken out of
 4 whoever's thoughts may have them.
 5 (Laughter.)
 6 DR. KATZ: And of course, that's exactly
 7 what I meant.
 8 MALE VOICE: I'll add also policy.
 9 DR. KROENKE: Dennis, and then John, and
 10 then the other two people.
 11 DR. TURK: This is just to clarify. Sharon,
 12 before you got here -- because you came a little
 13 bit late -- my introductory comments to the group
 14 specified very clearly that this was not designed
 15 to address regulatory issues, but rather to inform
 16 people of how to do the studies. So I tried to
 17 make that point in, and that should be in the
 18 record somewhere.
 19 DR. KROENKE: Good. Okay. John?
 20 DR. FARRAR: John Farrar, University of
 21 Pennsylvania.
 22 Bob, you talked about the purpose of the

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1 meeting. And I actually think that a tremendous
 2 benefit to the production of interesting studies
 3 moving forward would actually be to define the
 4 different types of situations in which opioid
 5 sparing are thought about and dealt with.
 6 If we think about the relationship between
 7 analgesics and addiction, there are different
 8 populations. The ones that got us into trouble
 9 were the young people who had their molars
 10 extracted and got 30 Percocet, and at the end of
 11 30, really liked the way they felt. Hopefully,
 12 that's not happening anymore.
 13 In the acute pain situation, clearly we want
 14 to limit side effects. TJ was just saying we want
 15 to limit potential respiratory depression. We want
 16 to do things. we want to use the lowest dose of
 17 the harmful medicines that we use; not just opioids
 18 but other things as well. So looking at that in
 19 terms of how we can spare those side effects or
 20 deal with those side effects is an important
 21 component of it. Whether I reduced the morphine
 22 dose over the 4 days that it's needed by 20 percent

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1 or 30 percent may not make any difference unless
 2 it's dealt with in terms of the side-effect profile
 3 that is dealt with there.
 4 Obviously, if we can get an opioid-sparing
 5 effect and we send people home without opioid,
 6 that's a good thing. You suggested that as a
 7 potential outcome; can we get them off sooner or to
 8 a lower dose sooner. So those I think provide some
 9 parameters to that.
 10 In the chronic pain situation where we have
 11 patients who are on chronic opioids already or who
 12 might benefit from chronic opioids, and there are
 13 such patients, then we want to think about the
 14 lowest potential dose possible for those folks.
 15 Those are generally not the abusers. Right?
 16 They're in general not the people who end up with
 17 OUD. They misuse occasionally and so on. And I'm
 18 not talking that there aren't any; there clearly
 19 are. But it's a different issue, and in that
 20 situation, opioid sparing and reduction of opioid
 21 might be a very interesting idea.
 22 One idea is let's just substitute every

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1 third pill as a placebo. There's very good
 2 evidence in animals that it works great. So there
 3 are ways to get around it. But the goal there is
 4 not to get them off the opioid necessarily; it's to
 5 make them better on as low a dose as possible.
 6 I guess the question that I have actually is
 7 targeted at Sharon, which is you actually said that
 8 you needed to take the population into account, the
 9 social benefits. And I guess I'm wondering which
 10 population we're talking about and whether there's
 11 been a discussion about those various populations
 12 we just spoke about, because I do think that from a
 13 societal perspective, way too many opioids are
 14 prescribed, too many in the medicine cabinet,
 15 et cetera. But that's not really about opioid
 16 sparing; that's about proper prescribing, proper
 17 treatment, and so on.
 18 So what group are we trying to think about
 19 when we deal with these things?
 20 DR. HERTZ: Just trying to think of where to
 21 start this because it's got a few pieces. When we
 22 make a regulatory decision, we have a number of

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1 elements to that decision-making. There's the
 2 proximate data that are in front of us, what is it
 3 telling us about the clinical trials; the way the
 4 drug was studied; the way the effects of the drug,
 5 both positive and negative, were demonstrated.
 6 We think about how that particular drug fits
 7 into the general availability of other therapies.
 8 We think about relative benefit, relative risk in
 9 an abstract kind of way because who wants things
 10 that are worse without any benefit to offset that
 11 worse in whatever way you want to characterize it?
 12 Then we also think about the big picture.
 13 When the first transmucosal immediate-release
 14 fentanyl for breakthrough cancer pain was under
 15 consideration for approval -- for those of you who
 16 are trying to remember which one that was, it was a
 17 raspberry-flavored, sugar-sweetened lozenge on a
 18 stick.
 19 MALE VOICE: Lollipop.
 20 DR. HERTZ: We don't use the L word.
 21 (Laughter.)
 22 DR. HERTZ: It's a lozenge on a stick. And

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1 the division, which predated me -- just so you know
 2 why I'm referring to it as the division -- had
 3 great concerns about what was going to happen with
 4 this dosage post-approval, and in particular,
 5 children.
 6 So that has nothing to do with the patient.
 7 It has nothing to do with the indication. It's
 8 fentanyl. We already know a lot about it. It was
 9 going to go out as a schedule II, but it was a
 10 population completely independent for the patient.
 11 That's one way we look more broadly.
 12 If somebody came to me and said -- us, not
 13 me, us. If someone came to a regulatory body and
 14 said we have this new opioid analgesic, it does not
 15 cause any constipation and it doesn't cause nausea,
 16 but it has the ability to impart tremendous
 17 reinforcing properties; although it would have to
 18 be scheduled II if it was going to be any schedule,
 19 it really looked different than comparators in
 20 those type of human-abuse liability studies.
 21 That product has to be considered from a
 22 number of perspectives, again, the proximate ones.

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1 But what is the impact of such an approval? Is
 2 there any way of preventing the widespread mayhem
 3 that could result from such an entity being on the
 4 market? And that's where we really start looking
 5 at the public health impact and the population in a
 6 broad way, because you can't make any of these
 7 decisions in isolation. You have to look at all
 8 the different levels that may be involved. And for
 9 some products, the public health impact is really
 10 not a major factor because little to no impact is
 11 expected.
 12 If I have an application for a different
 13 formulation of an existing product that has a
 14 similar PK profile, that's not quite the same thing
 15 as that completely hypothetical situation that I
 16 described, which could be quite harmful from a
 17 public health perspective.
 18 DR. FARRAR: And where does opioid sparing
 19 fit in? I like that description, and it makes it
 20 very clear. And I remember Actiq and all of the
 21 discussions about that, and there were some real
 22 serious concerns, and still are.

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1 Where does opioid sparing fit into that
 2 because it would help -- you raise the question of
 3 how much opioid sparing is clinically relevant, and
 4 I think to understand what we're targeting and
 5 ultimately doing would be helpful in knowing where
 6 to go with that.
 7 DR. HERTZ: It depends on what the specific
 8 program is targeting. Is the program trying to
 9 make the management of pain more tolerable from a
 10 global sense for patients? How does that impact
 11 the use of opioids in general? Is it really
 12 targeting replacing opioids with something that has
 13 a different safety profile, perhaps one that's not
 14 reinforcing?
 15 So there's no single answer, but I think
 16 it's a continuum, Bob, in particular, that reducing
 17 postoperative nausea and vomiting is one end of the
 18 spectrum. Reducing chronic endocrinopathy for a
 19 chronic patient is another piece of that. And
 20 lessening the amount of opioids in the medicine
 21 chest in the community is perhaps the furthest end.
 22 Then what I see as more of a parallel thing

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1 is in fact the development of novel non-addictive
 2 analgesics, which some people include in the
 3 concept of opioid sparing. But I have a harder
 4 time seeing that connection. It's still an
 5 important one, and its effect may be less need to
 6 prescribe other products, including opioids, but
 7 maybe it's got such a great safety profile that we
 8 don't have to worry about NSAIDs so much anymore.
 9 So there are bigger ripples than just
 10 opioids in the novel category.
 11 DR. KROENKE: Now, I'm going to take some
 12 questions from the group. You had your hand up
 13 here.
 14 DR. RATHMELL: Jim Rathmell from Brigham and
 15 Women's. Sharon, I think you really nicely
 16 clarified what you said earlier -- and this is more
 17 for the record so that we don't lose it. You said
 18 earlier, if we have these small changes in the way
 19 an opioid works that actually reduces analgesia for
 20 the patient but results in some small difference in
 21 the amount that gets out into society, you probably
 22 wouldn't view that very favorably because you're

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1 going to favor the patient in this one, the
 2 individual patient as you look for regulatory. But
 3 then if there's something broader that increases
 4 the risk to society, obviously it has to be weighed
 5 in. And I think that really came together nicely
 6 in this discussion.
 7 The other part is about what Bob has said.
 8 He's gone all the way to the extreme of opioid
 9 related deaths from prescription related opioids.
 10 That's probably not an outcome that we can measure
 11 in a meaningful way, but what we could look at is
 12 where there's a huge signal. And that's persistent
 13 opioid use in new users at a certain point in time.
 14 So I don't want to just say surgery because I think
 15 that's just limiting it. People get opioids for
 16 the first time, and they feel God's breath on them,
 17 as Eric has said, and they go on to persistent
 18 opioid use. And that's a pretty big signal, 6 to
 19 15 percent, depending on where you look.
 20 Maybe that's one of the areas where we can
 21 really work it into the clinical trials because if
 22 you have 10 percent of something in some

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1 population, that's very measurable, even in
 2 relatively modest sized clinical trials.
 3 DR. HERTZ: Can I just follow that question
 4 up?
 5 DR. KROENKE: Yes.
 6 DR. HERTZ: But what does that look like?
 7 Does that look reducing the amount of opioid use so
 8 that it's not producing those effects or does it
 9 mean replacing it with something else?
 10 DR. RATHMELL: It could be any of the above.
 11 It could be cognitive behavioral therapy. It could
 12 be brief interventions after surgery. It could be
 13 nonpharmacological or it could be pharmacological.
 14 But the outcome measure could be persistent opioid
 15 use 6, 12 months down the road. And if we have
 16 10 percent of a population that never used them
 17 before, had never been exposed before, and we can
 18 cut that in half with whatever it is, the
 19 intervention -- because we're looking broadly, not
 20 just at pharmaceuticals, but at other ways that we
 21 might approach this problem, and that could be a
 22 very meaningful outcome because it's very

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1 measurable.
 2 DR. KROENKE: So just a comment. I think
 3 it's clear that some of the kinds of issues people
 4 are bringing up lend themselves to an FDA type of
 5 clinical trial, and others are going to lend
 6 themselves more to an NIH type of trial in relation
 7 to things. So it's non-pharmacologic comparative
 8 treatments, if it's complex interventions, I think
 9 some will lend itself.
 10 Yes, sir? Back there? Name and where from.
 11 DR. C. BROWN: Yeah. Cole Brown, Innocoll.
 12 This discussion in tandem with something that was
 13 said earlier has made me think about one
 14 perspective of this opioid-sparing challenge that
 15 we have. It was mentioned that the FDA is working
 16 with sponsors to look at, based on their drug
 17 product, the basis for a difference in opioid
 18 consumption, what that means.
 19 I think the way the sponsors have looked at
 20 the 2014 guidance around the management of acute
 21 pain has been looking at the visceral versus
 22 non-visceral pain management aspect of postsurgical

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1 pain, and either correctly or incorrectly
2 interpreting that to evaluate soft tissue and hard
3 tissue pain, postsurgical pain. And within that,
4 looking at their drug products individually, so
5 looking at can they improve pain and reduction in
6 pain in a soft tissue pain model versus in a hard
7 tissue pain model, like a total knee arthroplasty.
8 I guess my question is to both Tong and
9 Sharon, that as we're thinking about these
10 different opioid-sparing measures, do we think they
11 will need to be specific to the individual
12 procedures or can they be in broader buckets? I'm
13 not trying to complicate things or saying I think
14 one way or the other, but the outcomes related to
15 opioid use might be a little bit different in a
16 patient who just had a total colectomy or bariatric
17 surgery compared to someone who had a breast
18 augmentation or something else superficial like
19 abdominoplasty.
20 DR. KROENKE: TJ, do you have any comments
21 about that, or anybody? Was it a question you had
22 or did you want those comments for the record?

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1 Because you spoke to that as well.
2 DR. C. BROWN: That was just a question on
3 should we think about -- the opioid-sparing
4 measures, should we be thinking about them in a way
5 that should be specific to different surgical
6 procedures or different patient populations.
7 DR. KROENKE: I guess maybe either one of
8 you, a short answer, and then I'm going to have
9 Eric makes some comments. In other words, is the
10 research design, or questions, or how we do it
11 different based upon procedure.
12 DR. HERTZ: I don't know. What is the drug
13 supposed to be doing and how does one demonstrate
14 it? And then you can determine if it has
15 something, a limited niche or a broad niche. I
16 don't know. It just kind of depends.
17 DR. KROENKE: Eric has some comments.
18 DR. STRAIN: I wanted to jump in. First of
19 all, I'm still a fish out of water 3 or 4 hours
20 later. But I'm enjoying being a fish out of water.
21 It certainly prompts me to think sort of outside of
22 the box.

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1 Pardon me?
2 DR. HERTZ: You're an amphibian.
3 DR. STRAIN: I'm an amphibian. Yeah. I'm
4 crawling out of the water --
5 (Laughter.)
6 DR. STRAIN: -- and gasping for air; story
7 of my life.
8 But it seems to me, as sort of an outsider
9 looking in on this, sparing is a strategy. And I'm
10 perhaps responding to Bob's question from 15 or 20
11 minutes ago now, because there are sort of two
12 domains of concern that strikes me of relevance, as
13 a strategy, to address either the problems t the
14 individual level or the problems at the societal
15 level. And I'm not necessarily raising anything
16 new. I think I'm just trying to crystallize my
17 thoughts about this.
18 Sparing at the individual level is trying to
19 address the adverse consequences that the
20 individual is having, as TJ and others have brought
21 up here. And it seems to me that that involves
22 ultimately lowering the dose of opioid that's being

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1 exposed. So if you can get them on a lower dose,
2 the individual, hopefully you'll have less of those
3 adverse consequences. And then how do you do that
4 is sort of the logical step there. Do you add in a
5 non-opioid analgesic? Do you use a device or
6 whatever in order to address that? And those seem
7 like ideas that could be pursued in.
8 Let me tangentially mention, this seems like
9 where the HEAL Initiative, wherever those to NINDS
10 guys went off to. This looks like the Clinical
11 Trials Network for pain, to me. This looks like
12 what they should be doing.
13 The second area of domain, though, is the
14 societal ones, which of course I highlighted in my
15 talk and I find of interest because that's the
16 diversion and misuse and overdose. And sparing
17 that decreases diversion, misuse, and overdose is
18 critical. And there, it's not really lowering the
19 dose; it's lowering the number of doses that are
20 being used that becomes critical. So it seems to
21 me there's sort of a bifurcation in strategies
22 because lowering dose is one set of trials, but

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

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

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

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

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1 DR. KROENKE: I'm not going to require
 2 anybody, but that's a good -- does anybody want to
 3 comment on that?
 4 DR. HERTZ: I think there are a couple ways
 5 one would have to look at the data for that kind of
 6 a product. There are reinforcing effects that are
 7 positive usually, and then there are the negative
 8 effects that can take away. We'd have to try and
 9 sort through that and look at the balance. I don't
 10 know what the actual answer is for something like
 11 that, but it's a very challenging problem. And
 12 I'll tell you where it's come up in a more
 13 proximate way.
 14 We had a product that went to advisory
 15 committee, so I can talk about it. It was a
 16 hydrocodone-acetaminophen combination with
 17 promethazine. And the idea was it would reduce
 18 nausea and vomiting. And trying to get a signal
 19 detection, the population was somewhat enriched for
 20 people who are likely to have that.
 21 one of the questions that arose was, if we
 22 take away the nausea, will people be more inclined

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1 to abuse this, and is it going to be more of a
 2 gateway drug? And we tried to look at it a couple
 3 of different ways, for a different reason because
 4 for promethazine has CNS effects. We worry about
 5 additive effects. When we told people to use less
 6 opioids, they started using gabapentinoid. So lo
 7 and behold, now everyone's worried about
 8 gabapentinoid. So we're trying to avoid some of
 9 these surprising, or perhaps not so surprising,
 10 events.
 11 That product was studied in a human-abuse
 12 liability study, and I'm actually not completely
 13 familiar with all of the details. It's been
 14 replaced by a lot of other products subsequently.
 15 But that comes up all the time; when you're looking
 16 at reducing symptoms, negative symptoms, what else
 17 happens?
 18 Some of the scales that are used, we look at
 19 these human-abuse liability studies, and we rely on
 20 them for a certain type of information. For those
 21 of you who aren't familiar, you take traditionally
 22 a non-dependent but experienced, what we call

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1 recreational opioid abuser, and you give them a
 2 couple of different things, and you have them rate
 3 it on a number of different skills. There's some
 4 qualification phase; it's not important right now.
 5 And they are asked to rate positive and negative
 6 effects.
 7 One of the scales that I particularly like
 8 is the use of a bipolar scale that has neutral in
 9 the middle, like it a whole lot at the top, and
 10 dislike it a whole lot at the bottom, which is a
 11 way to try and integrate some of these different
 12 things because we know that in certain
 13 circumstances, a product that can get you very
 14 high, which is one of the scales, you may not like,
 15 maybe because we put something irritating in it so
 16 that it would be nasty when you snorted it or what
 17 have you.
 18 So I think that kind of an assessment is
 19 really important when we start getting into perhaps
 20 opioids that have some of these properties.
 21 DR. KROENKE: Eric has a comment.
 22 DR. STRAIN: I like your question a lot,

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1 Mike. It strikes me that we kind of have that
 2 experience, which was barbituates and then
 3 benzodiazepines, and look where that got us.
 4 Right? So I'm not sure I want to pursue your
 5 product.
 6 (Laughter.)
 7 DR. KROENKE: Nat, comment, and then
 8 questions.
 9 DR. KATZ: I like the question a lot, too.
 10 It's very thought provoking. It also reminds me of
 11 the concerns people had about the HIV drugs when
 12 they came out because, oh, we're going to give
 13 people these HIV drugs, but then they're going to
 14 go be more sexually promiscuous, and that's morally
 15 evil, and we don't like that. So there was this
 16 very kind of theoretical anticipation of how many
 17 rungs outside of the patient, people's behavior,
 18 would be changed in some undesirable way.
 19 I think making treatments that work better
 20 for patients is a good thing. It's a societal
 21 good. It's a blessing when we can do that. And I
 22 don't think that these theoretical concerns should

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1 stop us, in particular, because -- and I'll ask
 2 Eric for his support on this --
 3 DR. STRAIN: I'm always behind you.
 4 DR. KATZ: -- thank you.
 5 We, for example, did a study of adolescent
 6 prescription opioid abusers a number of years ago
 7 and published it. And they were into snorting
 8 buprenorphine, and what they said was that they
 9 would snort buprenorphine, and they would look,
 10 hopefully, waiting for the moment where they would
 11 start vomiting because they knew after they started
 12 vomiting that they would start to feel high again.
 13 And you see all these examples where the side
 14 effects don't seem to bother people with drug
 15 addictions.
 16 So if you were to make one that was less
 17 nauseating or whatever, I think it would be a
 18 mistake to assume that that's automatically going
 19 to be like some kind of scourge on the planet of a
 20 new more abusable drug. So I say let's help the
 21 patients first.
 22 DR. GAN: Just another comment on your

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1 question and also Sharon's response, I think, to an
 2 extent, get to what Bob's earlier question is.
 3 There's a whole range of opioid adverse events.
 4 You've the annoying , unpleasant nausea, confusion,
 5 all the way to respiratory depression, and death.
 6 And I think that the drug, as Sharon mentioned, if
 7 it had been a drug that would reduce instead of
 8 nausea with a combination product, that it would
 9 reduce respiratory depression and death, I think
 10 the panel's response would be somewhat different.
 11 I think it also gets to that gradation of
 12 severity, know, how bad are the side effects and
 13 whether it causes death or not. And to that
 14 question, I think that it's a conundrum because
 15 know from the company perspective, they are trying
 16 to develop drugs that reduce maybe one of the
 17 opiate side effects, but at the same time, then,
 18 would it be open to more abuse? Now that they have
 19 no nausea, therefore they can use more of it. So
 20 it's an
 21 interesting question.
 22 DR. KROENKE: Why don't I do this? I'm

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1 going to do the last 5 minutes. I'm going to just
 2 allow people to get their comments or questions out
 3 [inaudible - off mic] by the panel, just because
 4 I'd like to maximize the number of issues that go
 5 on the record.
 6 So starting in the back, somebody had their
 7 hand up. So make your comments relatively brief
 8 for the record. Yes? Back there? Someone had
 9 their hands up. You had your hands up. Yes, right
 10 there.
 11 DR. SCHOLZ: Joachim Scholz, working at
 12 Biogen. Mike's comment is actually not so off
 13 reality. When I was still at Columbia University,
 14 we were working actually on a bias opioid receptor
 15 agonist that spares the Arestin via the
 16 [indiscernible] pathway; less side effects of the
 17 kind we have talked about, but the addiction
 18 liability is still unknown. It's a good analgesic.
 19 There are several of them in development.
 20 I think the main reason we have this
 21 workshop is really for limiting the addiction
 22 problems. So I think if we develop alternative

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1 opioids that spare some of these unwanted effects
 2 that patients feel immediately, it still doesn't
 3 solve the problem. And I would not considered that
 4 opioid-sparing strategy. I would just say it's a
 5 different opioid that we develop, but it doesn't
 6 solve the societal problem, and I think that needs
 7 to be considered when we talk about research design
 8 for opioid-sparing strategies. So they have to be
 9 long term that capture these other problems and not
 10 just focus on nausea, vomiting, or respiratory
 11 depression.
 12 DR. KROENKE: Yes?
 13 DR. MADSEN: I'm Torsten Madsen with
 14 Aptinyx. I just want to comment that I don't think
 15 the comment that Penny Cowan made on the patient
 16 perspective was addressed. Secondly, another
 17 comment that we have an awfully granular view of
 18 the side effects of opiates, and yet we accept that
 19 the view of pain in general is best measured with a
 20 scale that goes from zero to 10 and our view of
 21 that. So do we want to retain the same pain level
 22 in an opiate-sparing trial? Are we okay with just

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

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

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

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

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

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

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

21 (Applause.)

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

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

7 Thanks very much, Jim.

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

20 Thank you, Shannon.

21 Presentation- Shannon Smith

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

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

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

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

22 A scoping review is actually sort of new to

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

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

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1 You probably can't see all of this, but
 2 basically we excluded a lot of things because they
 3 didn't meet our criteria. They weren't clinical
 4 trials. They included children. But I want to
 5 highlight here that we were excluding people or
 6 excluding the clinical trials that were acute
 7 trials before 2010.
 8 We got a large number of acute pain trials.
 9 So to kind of narrow our focus for the acute pain
 10 trials, we focused on ones that were from 2010 and
 11 closer to the present, up to the present, and that
 12 still gave us 73. For chronic pain, we didn't have
 13 this limit because there were only 5 that were
 14 relevant, so we didn't have that same limit.
 15 Also, the steering committee provided some
 16 feedback about potential articles that could be
 17 relevant for acute pain and chronic pain, and in
 18 reviewing those, we found an additional 10 for
 19 acute pain and 17 for chronic pain. So we had a
 20 total of 83 acute pain trials, mostly
 21 postoperative. One was a postoperative study that
 22 went up to a year in its follow up. So you could

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1 start to argue that it's really chronic pain at
 2 that point; one severe acute pain in the emergency
 3 department study. The chronic pain trials, there
 4 were 22 articles that resulted in 22 studies, so
 5 there were some that were reporting multiple
 6 studies.
 7 So I'm going to start by talking to you
 8 about the acute pain trials, and again remembering
 9 that we're focusing on the methodological
 10 characteristics here; so what was done in a study;
 11 how did they do it; and how were they capturing
 12 opioid sparing in these studies?
 13 I wanted to start with the opioid related
 14 study objectives. For about half of these acute
 15 pain trials, the primary outcome was opioid
 16 sparing. For the other roughly half, opioid
 17 sparing was a secondary outcome. We thought opioid
 18 adverse events was the primary outcome in 2 percent
 19 of the trials, and I think in some ways this goes
 20 back to the point Nat was making about do we have
 21 this gestalt of all of these various AEs, in which
 22 case it might be really difficult to show any sort

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1 of movement because one person has nausea, the
 2 other person has vomiting and nausea and
 3 respiratory depression; how do you actually have
 4 any sort of assay sensitivity to look at
 5 differences in that way? These to actually focused
 6 on one particular adverse event, so they were
 7 somewhat unique. The rest of these, about
 8 two-thirds of them, were using opioid adverse
 9 events as a secondary outcome. It wasn't really
 10 the primary purpose.
 11 Again, this is probably hard to see all the
 12 details here, but the interventions and controls
 13 that were used in these studies, we lumped into
 14 this one first category, anesthetic protocol. Most
 15 of these were postoperative studies, so it was
 16 things like are they getting an epidural, regional
 17 anesthesia, blocks; those things were in that
 18 category.
 19 Then there were a lot of pharmacologic
 20 intervention, so NSAIDs -- I can never say this, so
 21 I call it dex; I think that's what other people
 22 call it, too -- antiepileptics, acetaminophen,

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1 some device behavioral, and then other that didn't
 2 really fall into anything else. There was one
 3 other trial that was nicotine that was given to
 4 patients.
 5 Controls. So over half of them were
 6 placebo-controlled trials; 17 percent were trials
 7 where it was the active intervention compared to
 8 some other intervention that either they thought
 9 was already being effective, was already shown to
 10 be used well in these patients. And that's a
 11 little bit different than this usual care medical
 12 management. There, the protocol or the studies
 13 were basically saying we compare this to usual care
 14 or medical management, which they either defined or
 15 did not, and then a variety of other kinds of
 16 controls.
 17 Who was included in these studies? Who were
 18 researchers enrolling here? As you could probably
 19 suspect, the biggest inclusion criteria was that
 20 the patient was having a specific kind of
 21 intervention, that they were having some sort of
 22 surgery, abdominal surgery, knee surgery, that sort

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1 of thing; and then a variety of other things like
2 how are they going to be in the hospital, what kind
3 of pain are they having. The ED study requires
4 that the acute pain be less than 7 days.
5 These two I think are interesting because as
6 I was talking with Bob about the results of this
7 scoping review, it dawned on both of us really that
8 Nat Katz always makes the point that when we're
9 doing these studies and wanting to look at things
10 like opioid sparing, we often don't include the
11 people for whom opioid sparing might be an outcome
12 of interest.
13 Here, these are acute pain studies. These
14 are people who are coming in for surgery. They're
15 at least trying in these two studies to recruit
16 people who are on opioids in some way. So that's
17 great but also contrasted into the exclusion
18 criteria that these acute pain trials were using.
19 So they were excluding people if they had opioids
20 or other substance misuse or abuse; opioid
21 dependence or withdrawal symptoms; chronic pain
22 conditions or selected chronic analgesics; using

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1 opioid analgesics.
2 So they're excluding the people for whom we
3 would want to know are these treatments actually
4 going to benefit them. That's sort of a problem if
5 we're going to be able to understand if these
6 treatments work in the broader population.
7 What were the primary outcomes? How are
8 they getting at what they care about? Opioid
9 dosage as a continuous variable was the primary
10 outcome in 39 percent of the trials, and then some
11 of variations on that. Opioid dosage and pain were
12 the two primary outcomes.
13 This one is opioid reduction, so they just
14 dichotomized. They came up with some number that
15 they wanted to decide was the appropriate amount of
16 reduction, and either people met that or they
17 didn't. Then they also a couple of studies looked
18 at opioid adverse events, so either self-report
19 measures or observed by the study staff, or pain
20 outcomes were a major -- 13 percent of the studies,
21 so maybe minor would be more accurate, in these
22 acute pain trials.

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1 For secondary or exploratory outcomes,
2 opioid dosage, again, was frequently used in about
3 half of the trials. Time to first opioid dose was
4 also an outcome of interest in these studies, and
5 then opioid reduction in a dichotomized way. Then
6 one study did an ordinal, like did people take
7 zero, 5, 10, or more than 15 milligrams? And this
8 one, did they go home with an opioid dosage when
9 they were being discharged from the hospital?
10 For opioid adverse events, most of the
11 studies that were capturing opioid adverse events
12 weren't reporting how they did that. And again,
13 methodologically, that's problematic because we
14 can't compare from one study to another. We can't
15 say, hey, this drug is having these effects on
16 people and it's being assessed in this way, and
17 compare that to another study.
18 Of those that did report what was happening,
19 it was either observed. People were being asked
20 did you have this symptom, did you have this
21 symptom, did you have this symptom, and the patient
22 just answered yes or no. In 7 of the studies, they

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1 were looking at charts to see were antiemetics
2 prescribed, were laxatives prescribed, and using
3 that as a signal that the person was having opioid
4 related adverse events; self-report measures also,
5 and then passive capture, just having patients
6 describe what sort of side effects they were
7 having. Then again, pain was being assessed in a
8 lot of the studies as well, or a proxy for pain,
9 and then time to discharge from the PACU was a
10 secondary outcome in two of the studies.
11 In terms of this how are we assessing opioid
12 dosage, how is it being captured, I actually was
13 thinking the same thing as Jennifer Haythornthwaite
14 was just saying. Acute pain trials have this huge
15 benefit that they have people in the hospital. So
16 there are very few not reported's that were in
17 these trials. They were able to tell how the
18 opioid dosage was captured. So 43 percent was the
19 PCA; 41 percent, it was either being administered
20 by the study staff are they're recording what the
21 patients were taking. They had a real controlled
22 way to assess that; and other variations, so

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1 combinations of different things were used as well.
2 How were the opioid adverse events measured?
3 Two studies used a nausea NRS. One was a zero to
4 10 and one was zero to 5; the Bristol Stool scale;
5 the opioid related symptom distress scale that I
6 think Dr. Gan talked about before; opioid side
7 effects scale; and then this confusion assessment
8 method for measuring delirium in one study.
9 Before I tell you about the clinical
10 relevance as discussed by these studies -- I'm not
11 going to make any conclusions about the clinical
12 relevance. I'm going to punt like Sharon Hertz did
13 on that question. I'll tell you what they said
14 about whether or not their results were clinically
15 relevant, but I think it's important for us to kind
16 of take a step back for a minute and think about
17 what kind of clinical relevance we really care
18 about.
19 Do we care about what's happening within
20 patients? So my opioid dose goes down by a certain
21 number of milligrams and I'm feeling a lot better,
22 and that's meaningful for me. Do we care about

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

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

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1 This first article referenced a review that
2 showed that Cox-2 inhibitors reduced postoperative
3 morphine use by 10.9 milligrams, and therefore the
4 reduction that they saw in their study was
5 clinically meaningful. No comment on the
6 difference between groups, but comment on within
7 patient difference and in reference to a review of
8 Cox-2 inhibitors. So again, we can take from that
9 whether or not that's relevant.
10 This article talked about -- they referenced
11 an article that had the median effective analgesic
12 dose of an antiepileptic, and the median effective
13 dosage of that antiepileptic decreased morphine by
14 greater than 30 percent. So they basically used
15 that to claim that a reduction in morphine use of
16 30 percent or more was clinically meaningful.
17 This article cited their own prior research
18 showing that 10 percent reduction in -- I can't
19 remember what the drug was now, was clinically
20 meaningful. But they did in this case acknowledge
21 that it was a clinical judgment, so, again, take
22 from that what you will.

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1 This one I find very interesting. This
 2 article indicated that a reduction in the PCA usage
 3 of greater than 30 percent is clinically
 4 meaningful, and then went on to cite references
 5 that it's clinically meaningful because pain
 6 reductions of 30 percent or more are clinically
 7 meaningful. I guess it's a leap to make that
 8 conclusion --
 9 (Laughter.)
 10 DR. SMITH: -- at the very least.
 11 MALE VOICE: [Inaudible - off mic].
 12 (Laughter.)
 13 DR. SMITH: Strangely, it wasn't even citing
 14 John Farrar's paper, actually. We can't count it
 15 at all.
 16 Then in this final one, they had a reference
 17 to explain why they said that a 30 percent decrease
 18 in oxycodone was clinically significant. But then
 19 when I looked at the reference, there was no talk
 20 about oxycodone. There was no talk about clinical
 21 meaningfulness, so sort of useless and irrelevant.
 22 That's the lay of the land, as I have been

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1 saying, for acute pain. I want to focus now on the
 2 chronic pain trials because there are a few minor
 3 differences as you'll see. Again, for the study
 4 objectives, opioid sparing was the primary purpose
 5 in about a third of the trials and the secondary in
 6 about 42 percent of the trials. Opioid adverse
 7 events were always a secondary if they were
 8 included, and it was in about a third of the trials
 9 as well. And then 19 percent included opioid
 10 misuse, abuse, or withdrawal as a secondary or
 11 exploratory outcome.
 12 Again, there's a lot going on here, but in
 13 terms of interventions, a lot of pharmacologic, but
 14 then a few other behavioral things pop in there;
 15 behavioral, this multidisciplinary care. So
 16 they're seeing MDs and behavioral health, and maybe
 17 other kinds of treatment as well. Then for the
 18 controls, here we see a lot fewer placebo controls,
 19 but we do see a lot more comparison to other
 20 opioids. So people are kind of staying on the
 21 opioid that they're on, and then they're
 22 randomizing the other people to something else; and

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1 then usual care or medical management, different
 2 dosages of the same intervention, and some other
 3 controls as well.
 4 Who's being included in these studies?
 5 Here, it actually was much easier to lump these
 6 into opioid related and pain related. Here, they
 7 were including people who are on opioids. These
 8 are people that they want to spare the opioids
 9 because they're probably already taking opioids, so
 10 minimum length of time that they're using the
 11 opioids around the clock; something about their
 12 dosing; that they are having dependence or
 13 withdrawal symptoms; and then also pain related
 14 inclusion criteria, that they have some minimum
 15 pain intensity or maximum, that their pain is
 16 poorly controlled. About half of them also had to
 17 have a specific pain condition to be in the study,
 18 although that wasn't true of all. Some were just
 19 chronic pain in general.
 20 For exclusion criteria, here half of the
 21 trials were excluding people if they had
 22 psychological or psychiatric disorders, again,

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1 raising that question about is this opioid-sparing
 2 literature reaching the people for whom we might
 3 want to be offering opioid sparing? And again,
 4 here with about a third of the trials excluding
 5 people if they had opioids or other substance
 6 misuse or abuse.
 7 This one is a little bit weird. Here they
 8 couldn't be using any other analgesics other than
 9 what was in the study, so they had to convert to
 10 the opioid that was in the study in order to be
 11 included.
 12 So what were the primary outcomes in these
 13 studies? Here, opioid dosage was the primary
 14 outcome in a about a quarter of the studies, opioid
 15 dosage and opioid AEs. One study included both of
 16 those is primary outcomes; some opioid misuse and
 17 abuse or withdrawal studies, and then pain in about
 18 a third of the studies was the primary outcome, and
 19 then some other things too. There was one study
 20 that seemed to be essentially a pilot, and it was
 21 looking at whether or not people would stay in a
 22 treatment protocol where they had to come off their

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1 opioid altogether or switch to buprenorphine, I
2 think was that study.
3 Secondary outcomes, so opioid dosages being
4 captured as a continuous variable in about a third;
5 a dichotomized opioid reduction in 15 percent.
6 Time interval between opioid doses, so are people
7 able to go a longer length of time between their
8 opioid doses? Then again, we're not seeing real
9 excellent reporting of the opioid AEs in these
10 trials either. Some self-report questionnaires
11 were being used; observations in one study; passive
12 capture where people just wrote down what they were
13 feeling in one study. Opioid withdrawal and misuse
14 and abuse, and I'll show you the measures used for
15 that in a minute. Pain was a secondary or
16 exploratory outcome in 81 percent of the trials.
17 This one I wanted to point out on its own.
18 Russell Portnoy had a study where, as a secondary
19 outcome, he was doing a composite of pain and
20 opioid dose, where it kind of mimics some of the
21 things that we've been talking about here today.
22 So if your pain stayed constant but your opioid

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1 dose decreased, then that was considered a win. If
2 your opioid dose stayed constant but your pain was
3 decreasing, then again, that was considered a win.
4 He was trying to bring these things together
5 because I agree with Nat's point that we also need
6 to be thinking about what's happening with the pain
7 management.
8 How was opioid dosage captured? Unlike the
9 acute pain trials where they had people captive,
10 here, self-reports were the most frequently used
11 method. Twenty percent of the trials didn't report
12 what was being done. There was one severe cancer
13 chronic pain trial that used patient-controlled
14 analgesia; that completion of the opioid
15 discontinuation or opioid replacement treatment; a
16 number who were taking their opioid rescue during
17 study visits.
18 It was really not very clearly written, but
19 it seemed like they were only capturing it when
20 they came in for study visits, so I'm not really
21 sure about that; that they got an IV dose during a
22 procedure or there was one study done where they

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1 were looking at earning oxycodone doses versus
2 earning money and use that as a way to kind of
3 capture. So it was being captured clearly by the
4 study staff.
5 How were the opioid related adverse events
6 measured? Opioid withdrawal symptoms were
7 collected in 4 of the trials. The Clinical Opiate
8 Withdrawal Scale was used in two of the studies,
9 the Subjective Opiate Withdrawal scales in one;
10 some self-reports and observations of physiological
11 symptoms in another. Misuse and abuse was measured
12 by the current opioid misuse measure, the
13 Prescription Opioid Misuse Index.
14 Then actually, I think this might have been
15 one of your trials, Dr. Jamison, drug misuse index
16 that uses a triangulation method. They collect
17 urine, they use the COMM and they use the PDUQ to
18 see if people qualify as misusing their
19 medications; and then constipation as an NRS in 3
20 of the trials.
21 So here, there was not much discussion,
22 again, of the clinical relevance of the results.

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1 Again, about three-quarters of the studies didn't
2 discuss it at all. And those that did, none of
3 them provided any references. None of them talked
4 about it in terms of their sample size
5 calculations. It was always in reference to the
6 results. Four of the studies said that their
7 results were meaningful, no reference; two studies
8 said that their results might be meaningful, no
9 references; and one said they were not meaningful,
10 again, no references.
11 To sum up all of this, I think it's
12 important for us to know this landscape, to
13 understand the lay of the land, as I've been
14 saying, so that we can understand what's being
15 done; how are we assessing adverse events; how are
16 we assessing opioid sparing, so that we can then
17 make better recommendations as a consensus group to
18 move forward and think about what should be done or
19 maybe what more research we need to be doing.
20 That's the first point.
21 I think the other key point we need to be
22 thinking about, is it good to be excluding patients

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1 who might most be in need of the opioid sparing or
2 an opioid adverse event reduction? If we decide
3 that that's not ideal, then how can we include them
4 in a way that doesn't put them at risk? We also
5 have to be thinking about that.
6 What's clinically meaningful, both within
7 patient and between groups, and potentially
8 societally? I also agreed -- I think this is a
9 really important point -- that we need to capture
10 opioid sparing and/or reduction of opioid adverse
11 events, and pain because although I am thoughtful
12 about Dr. Gan's presentation, where I'm willing to
13 take a little bit more pain if my opioid adverse
14 events reduce a whole lot, but I do think that we
15 at least need to consider these things not in
16 silos. Like they all kind of are related together,
17 and it's important for us to consider them
18 together. Thank you, guys.
19 (Applause.)
20 DR. RATHMELL: Brett, while you make your
21 way up here, let's take a question or two,
22 comments. Michael?

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1 DR. ROWBOTHAM: Were any of the chronic pain
2 studies, either exclusively or include an arm where
3 patients just withdrew from opioids completely
4 rather than a substitution strategy like converting
5 them to buprenorphine?
6 DR. SMITH: Maybe one of them. Other than
7 that, it looks like they were all being converted,
8 at least in the ones that were included in the
9 scoping review.
10 John, do you have a point relevant to that?
11 Oh, okay. So yeah, not that I remember, at least
12 in what we found in our scoping review.
13 DR. MARKMAN: John Markman. [Inaudible -
14 off mic].
15 DR. SMITH: I'm trying to think back. We
16 didn't specifically code for that, so I don't -- it
17 doesn't ring a bell because Jen and I weren't
18 looking for that when we were coding the articles.
19 It's possible that it was there, and we just
20 weren't looking forward, so I'm not remembering it.
21 DR. RATHMELL: Thank you very much.
22 DR. SMITH: Thank you.

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1 DR. RATHMELL: Next is Brett Stacey, who's
2 professor of anesthesiology and pain medicine at
3 University of Washington and the medical director
4 of the Center for Pain Relief at the University of
5 Washington. He's going to talk about assessing
6 opioid use and opioid outcomes.
7 Presentation - Brett Stacey
8 DR. STACEY: Good afternoon, everyone.
9 Thank you for inviting me, Bob and Dennis. And
10 even though Bob said we weren't going to talk about
11 grammar and things and punctuation, and as the
12 hyphen variably appears. So I put mine in
13 parentheses. If you liked the hyphen, feel free to
14 think it's there.
15 (Laughter.)
16 DR. STACEY: That's the first thing.
17 The second thing, I thought I'd start with a
18 little vignette that kind of motivates me a little
19 bit in this area, which is I know a person who was
20 not prescribed chronic opioids, did have a
21 psychiatric crisis, was able to gather up dozens of
22 opioids from prescriptions that had been given to

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1 various members of the household, and instituted an
2 overdose plan to end their life, and thankfully
3 revealed the plan to someone who then intervened,
4 and didn't happen. But dozens of opioids were
5 found in the household. All have been prescribed
6 for an acute pain condition and then barely used
7 and hoarded.
8 So we need to think about this. It's not
9 just the chronic pain patients we might be
10 impacting.
11 If you're an anesthesiologist of a certain
12 age, you may remember this study. I remember it
13 really well because I was very young and
14 impressionable when I read this, and it really
15 influenced me a lot, because at that time I was
16 thinking of myself as an anesthesiologist, which I
17 no longer do. But at the time I did, and I thought
18 this is an amazing study because it shows that your
19 anesthesia technique can influence the pain
20 experience for a long time thereafter. with a short
21 little intervention.
22 What this was, was an anesthesia technique

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1 study looking at a double-blind, randomized trial,
2 general plus local infiltration versus spinal. And
3 the main focus of the paper was pain at rest, pain
4 with pressure, and pain with movement up to 10 days
5 after a hernia repair. And here's this data, and
6 this is why I got really excited about this.
7 Ten days later, you can tolerate more
8 pressure at the site, and you have less pain with
9 more pressure, which means things like putting your
10 seatbelt on would be less painful. So this has
11 real-world implications. It wasn't until a few
12 years later when I went back and looked at this
13 paper again, that I discovered this outcome in
14 there, which is as a marker for the duration of
15 analgesia, they looked at the first opioid dose and
16 showed a huge difference with the local anesthetic
17 group versus general anesthetic; so a big delay in
18 use of opioids.
19 But like many, many, many acute pain
20 studies, here's one outcome endpoint that shows a
21 reduction in opioid dosing, initially, but did they
22 go home with fewer opioids? Did they catch up the

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1 net right after they got the first dose? None of
2 that stuff is reported, so it's just kind of out
3 there as a single outcome point, and that's like a
4 lot of the studies that we're going to look at.
5 Some things are really obvious, but they get
6 stated anyway, and here's an example of that. My
7 first visit to the Seattle Zoo with my son, loved
8 this, and he said, "Whoever would want to pet a
9 porcupine?"
10 (Laughter.)
11 DR. STACEY: Which, I don't know, but here
12 we are.
13 So I'm going to say some things that are
14 obvious, and one of these is a little bit
15 controversial. Opioid reductions are often not the
16 focus of the study, and the data can be buried like
17 in that first study I showed. In general, I think
18 most patients, except for the trade-off of side
19 effects, would say opioid reduction is meaningless
20 if pain is worse, unless you have some other
21 benefit that would overcome that.
22 For acute pain, there's really no standard

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1 of how to assess opioid use, the dose reduction, or
2 opioid specific outcomes, but there are a lot of
3 studies that report opioid sparing. And for
4 chronic pain, there's even less consistent data, as
5 we heard the last half hour. And even though
6 there's not tons of data, there is a lot of
7 discussion about it. This is a hot topic.
8 This is an old paper, but you might
9 recognize an author or two there, saying, "Who
10 cares about the number of milligrams?" And then
11 here's a more recent one saying, "Should hospitals
12 market their opioid-sparing analgesia to patients?"
13 Of course this is in the anesthesia literature.
14 And then this is a good one to think about; "Opioid
15 omission is not opioid sparing." Just because you
16 don't give someone a dose of medication doesn't
17 mean you spared them something. It means you may
18 have forgotten something.
19 (Laughter.)
20 DR. STACEY: And this one says, "Oh yeah.
21 We should go ahead and market this." So there's
22 lots of back and forth here, and it's not settled

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1 out there in the world whatsoever.
2 I am not going to talk about the pain
3 outcomes thinking there's been 20 IMPACT meetings
4 about that, or something; maybe 19 of them. So
5 instead, I'm going to talk about how do they assess
6 the opioid use in these clinical trials and what
7 should we think about as standards going forward?
8 So I'm just going to review some of the stuff, and
9 then we can have discussion later about which ones
10 we think are important or not important.
11 A very commonly important one is time to
12 first dose or the use of a rescue medication. Then
13 there's the dose prescribed, how many pills were
14 prescribed per event or time period; number of
15 pills or doses taken. Then there's something
16 looking at the accounting for the total dosing, MME
17 or MED, or accumulative daily dose.
18 We will talk about those first three in more
19 detail. Then there's duration of opioid therapy,
20 opioid refills, does the dose go up? And then
21 there's the special case of a dose of zero, a dose
22 of zero meaning you're tapered off or you

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

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

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

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

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

11 There's MED mentioned, a whole bunch of
 12 stuff about how to calculate it. There's an online
 13 dose calculator that has controversial dosing a
 14 equivalence for methadone, and fentanyl, and
 15 others. I'm sure pretty much every state has some
 16 mention of MED or MME somewhere or another. So
 17 it's often reported per time period, which is often
 18 daily, or else totaled over the whole study. So if
 19 it's a 5-day study, they may say over the whole
 20 5-day period, here's the MED.

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

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

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

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

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

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

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

20 (Laughter.)
 21 DR. STACEY: The review of studies
 22 demonstrated opioid sparing for adjuvant

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1 medications, regional anesthesia, and nerve blocks,
2 and went through a bunch of studies showing opioid
3 sparing. And by far, the most commonly reported
4 outcome was reduced opioid consumption the first 24
5 to 48 hours, usually totaled MED/MME kind of thing.
6 And that's how they determined there was an
7 opioid-sparing effect.
8 I love their conclusion. "While individual
9 pieces of optimal postoperative pain management
10 plans have been studied, long-term outcome data are
11 lacking, as well as data regarding rebound pain.
12 There is much work to be done." I forgot to close
13 the quote, but "There is much work to be done."
14 Yes, and I think that's why we're here. There is
15 much work to be done in this area.
16 So I thought I would look at a few studies,
17 acute pain studies. These are not exhaustive
18 because, as you heard from Shannon, there's 80
19 acute pain studies, which she was able to identify.
20 There's a whole bunch, but here's one, which is a
21 phase 3, multicenter, double-blind, placebo-
22 controlled, randomized trial of a drug with a whole

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1 bunch of subjects, with everybody getting the exact
2 same operation, the very well studied bunionectomy.
3 Everybody loves that bunionectomy model.
4 All patients had standardized anesthetic
5 approach and initial analgesia with a popliteal
6 sciatic block and a metatarsal block. The study
7 medication was not given until after the first day,
8 interestingly, then they're randomized to different
9 doses of the study drug, celecoxib or placebo. And
10 they had a whole bunch of outcome measures: pain
11 intensity difference; treatment groups; placebo;
12 proportion of patients who used rescue; time to
13 first use of rescue; number of tablets used.
14 So the results were the active treatment
15 resulted in reductions are most pronounced after 24
16 hours and did not extend beyond the 48-hour period.
17 So I had a lot of thoughts about this, which will
18 come up as we look at these tables. So there's
19 zero to 24 hours when there's no study drug being
20 done; it's just the groups before they're given the
21 study intervention. If you can at what the little
22 tiny writing at the bottom says, it's the

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1 proportion of patients who received rescue
2 medication in the first and second 24-hour period.
3 Basically, a lot of people got rescue
4 medication before they got the study drug. They're
5 given the study drug, and if you got placebo, it
6 helped because pain subsides after a bunionectomy,
7 after 24 hours. But it didn't help as much as the
8 active treatments. That shows some opioid
9 reduction there.
10 This one looks at the number of actual
11 rescue medications that were given to the groups as
12 a whole at the top, and then the groups by those
13 who receded study medication. So it looks like it
14 reduced your chance of getting a rescue drug more
15 than if you're in any of the groups that got a
16 rescue medication, and didn't necessarily reduce
17 how many rescue meds it got in any meaningful way.
18 So there's a study that report some opioid sparing.
19 It stops at 48 hours. I don't know what they went
20 home with after that.
21 Here's one that TJ could comment on a lot
22 more than I am, but I'm going to still present it.

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1 This is a secondary outcome, so it's looking at two
2 studies together for abdominal pelvic orthopedic
3 surgery for an intervention with an active control
4 and then a placebo, a whole bunch of subjects, 608
5 subjects. Intervention was the IV
6 anti-inflammatory, a placebo dose adjusted by
7 non-pain factors; several opioid assessments;
8 proportion of patients requiring opioids; and
9 cumulative opioid dose over the 5-day study period.
10 So multiple ways to look at the treatment
11 groups getting less opioids were discovered in the
12 end. This is a secondary paper, but a good one
13 because it had some interesting information in it,
14 so here we go. This basically shows compared to
15 placebo, a lot fewer people required opioids. And
16 if you look at the cumulative dose, it's less; so
17 many ways of reporting this. This is a different
18 way. And this is saying, hey, we collected a lot
19 of data. Let's break it out separately and report
20 it separately from the primary outcomes from the
21 study. I think it's helpful.
22 This is a different environment. This is an

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

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

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

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

5 This one is looking at the duration of
 6 analgesia, which was assessed as kind of their
 7 first request for pain medication or pain score of
 8 4 or -- moderate to severe range of pain. They had
 9 a whole bunch of measures looking at duration of
 10 analgesia and motor block, et Cetera, and basically
 11 showed that there was in the active treatment
 12 groups decreased opioid dosing, and patients were
 13 more satisfied with that decrease opioid dosing.
 14 So it's reported lots of different studies, lots of
 15 different ways.

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

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1 painful thing.

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

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

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1 TJ talked a little about enhanced recovery
 2 after surgery programs, a while ago, it used to be
 3 preemptive analgesia and preventive analgesia, and
 4 then the term was multimodal analgesia, and now
 5 it's really more enhanced recovery after surgery
 6 for the most part, which my version of describing
 7 what that is, it's many interventions, a
 8 systematic, multifaceted team approach spanning the
 9 perioperative period with multiple objectives.

10 Improved pain control is not the sole focus. The
 11 goal is to get the patients out of the hospital,
 12 keep them out of the hospital, and not have them
 13 come back, and recover faster. And somewhere in
 14 there is pain and opioids.

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

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1 helpful, I said, "Yes. Look, there's opioid
 2 reduction in all these areas but doesn't really go
 3 into any details whatsoever." I'm not going to go
 4 into any more detail on this. TJ covered it a bit.
 5 Then there's this whole issue about the
 6 opioids actually prescribed for surgery, and this
 7 kind of gets back to my initial vignette of the
 8 person who gets in desperation and is able to find
 9 dozens of opioid doses around the household. These
 10 are a whole host of studies that showed that a
 11 large proportion of medications prescribed in the
 12 acute perioperative period are never used, which
 13 means they hang out available for unmonitored use
 14 at some future date. And they've shown that
 15 persistent opioid use is just as likely after minor
 16 versus major surgeries, as we saw this morning.
 17 Then if you prescribe less, you still have happy
 18 patients.
 19 So it is amazing to me how these
 20 opioid-reducing claiming studies don't look at the
 21 actual opioid prescriptions for the most part.
 22 These are studied like in separate areas. We

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1 should put them together potentially.
 2 Now, I want to talk about chronic pain.
 3 There was a Cochrane review in 2017, handily,
 4 looking at interventions to reduce prescribed
 5 opioid use in chronic pain. They were able to
 6 identify 5 studies that the populations are quite
 7 heterogeneous, as were the interventions and the
 8 outcomes reported. And they decided what a
 9 responder was. They decided to look at responders.
 10 At least a 50 percent reduction in opioid
 11 consumption was part 1, or complete opioid
 12 withdrawal, or reduction below a high dose. So if
 13 your dose was above 120 MED, and you're reduced to
 14 now under 120 MED, that was considered to be a
 15 responder as well.
 16 A responder also had to have, at worse, no
 17 increase in pain as a result of the intervention.
 18 Both aspects of improvement had to be maintained
 19 for at least 3 months post-intervention. So back
 20 to the question about how long does a study have to
 21 be? At least 3 months for this review. I looked
 22 through this, and, really, opioid use was not

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1 assessed in any kind of common way. It was really,
 2 really vague how it was assigned. And all the
 3 other outcomes, which we've addressed in every
 4 other IMMPACT meeting, were inconsistently
 5 reported.
 6 My conclusion is nothing really helpful
 7 here. We can improve the literature really easily
 8 as a group by coming up with some studies here. My
 9 second conclusion is 50 percent reduction in opioid
 10 dosing is a pretty high bar. Is any reduction
 11 meaningful? Does it need to be 20 percent, 30
 12 percent? It's a thing we should discuss, but 50
 13 percent seems high, and we really think that
 14 IMMPACT guidelines should be used for outcomes.
 15 They kind of go on to say, yeah, there's a
 16 lot of limitations, there's a lot of work to be
 17 done. You can read this at your leisure later.
 18 And it talks about the multiple other outcomes
 19 we've talked about a little bit, about mood, social
 20 functioning, personal role functioning, et cetera,
 21 as important to look at.
 22 This is another review equally revealing of

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1 deficiencies. They identified 61 studies. They
 2 found quality was good in 3, fair in 13, and poor
 3 in 51. One of the good studies did not really have
 4 opioid reduction as a primary objective, so it's
 5 not so exciting; multiple limitations. And their
 6 conclusion was very low quality evidence suggested
 7 several types of interventions may be effective to
 8 reduce or discontinue long-term opioid therapy, and
 9 that pain, functional, and quality of life may
 10 improve with opioid dose reduction; really a
 11 strongly worded, powerful conclusion.
 12 I thought I'd just look at a couple of
 13 random things, so this is looking at -- this is not
 14 really a clinical trial up front, but it is an
 15 intervention. This is from Pacific Northwest
 16 looking at education and policies, a double dose is
 17 better. That's my summary of what the name of the
 18 study is.
 19 The Washington state guidelines basically
 20 came up with this new high-dose idea of
 21 120 milliequivalents. It was before I lived in the
 22 state of Washington, so I have nothing to do with

1 it. It was basically published in 2007 and became
 2 more or less law and regulations in 2010. This big
 3 cooperative group added additional initiatives in
 4 education for their providers. They also had
 5 providers who were contracted providers, who did
 6 not get the additional education information about
 7 opioid reduction.
 8 What they did in this study was they
 9 compared the group that got not just the state
 10 regulation but also their internal education and
 11 policies and reinforcement of the state policies
 12 versus those that just got the state policies.
 13 That included quite a few patients, 16,653 for the
 14 group practice and 5,552 for the contracted people.
 15 They looked at MED plus people who got
 16 excess drugs, and there was definitely greater
 17 reduction in the group that got the double-dose of
 18 education. So their own providers did a better job
 19 than those who are contracted. And this kind of
 20 shows the trends over time of the doses coming
 21 down. This is the percentage of patients getting
 22 high dose in this first study, in this first graph,

1 opioids in a chronic pain patient receiving
 2 interventions for pain treatment.
 3 There are really a whole host of factors in
 4 there that might limit that, ranging from
 5 procedural factors. The study factor is not
 6 designed to do that; social, biologic,
 7 pharmacologic, psychological, and medical, a whole
 8 bunch of things associated with being on chronic
 9 opioids in the first place and then not being able
 10 to reduce the dose. That was a nice review.
 11 Some conclusions. For acute pain, pain
 12 satisfaction and function outcomes will be
 13 discussed of course elsewhere in other IMPACT
 14 things. Acute pain studies report a whole bunch of
 15 outcomes, but there are a lot of outcomes that may
 16 have meaning, but those that extend beyond the
 17 immediate post-op period are rarely reported, and
 18 we need to really encourage that, in my opinion.
 19 Chronic pain MED is by far the most common
 20 reported variable. High-dose patients using MED is
 21 often reported as an additional complaint. Getting
 22 patients all the way to office is also a complaint,

1 and this is those, about the average dose, how it
 2 decreases.
 3 So they're pretty close to each other at the
 4 beginning, then there's separation out. So this
 5 would imply that getting education is potentially
 6 an effective dose reducer.
 7 MALE VOICE: [Inaudible - off mic].
 8 DR. STACEY: Pain scores were not reported
 9 in any consistent way. That was not their goal.
 10 Here's a review looking at interventions.
 11 For those of us who do procedures, we think
 12 procedures are fantastic. They just take away all
 13 the nociceptive input, and pain goes away. It
 14 melts away, and you don't need opioids anymore.
 15 Basically there aren't any intervention
 16 studies for opioid reduction as the primary outcome
 17 for chronic pain. The data to support opioid
 18 reduction is, quote, "very limited," which I would
 19 say translates to nonexistent. The best thing of
 20 this paper is this, which you may not be able to
 21 digest really super fast, but it's the myriad of
 22 factors that may make it difficult to reduce the

1 and there are many challenges to actually
 2 conducting a chronic pain study for opioid
 3 reduction and opioid sparing.
 4 The unanswered central question is basically
 5 what opioid dose outcome must you have in order to
 6 say this is indeed opioid sparing for both acute
 7 pain and chronic pain? Because right now, anybody
 8 can claim it, as far as I can tell. You can just
 9 say, oh, we've reduced opioids because we had one
 10 of some random outcome that was good. So if we can
 11 define what we think it is for the opioid dosing
 12 that counts, then that would be a positive step
 13 forward.
 14 I tried to finish a couple of minutes early,
 15 and I think I did. Any questions?
 16 (Applause.)
 17 DR. FARRAR: Brett, a great review of the
 18 topic and raising some very interesting points.
 19 DR. RATHMELL: Name?
 20 DR. FARRAR: I'm sorry. John Farrar,
 21 University of Pennsylvania. I'm forgetting who I
 22 am.

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1 You started off with a story, and that is
 2 the story that is very often presented at FDA
 3 hearings where opioids are being considered, "My
 4 son went to a party and took a dose of something
 5 and died." And my question to you is, would any of
 6 the things you mentioned in terms of opioid sparing
 7 have an influence on that? Because to me,
 8 honestly, it sounds like a procedure issue, which
 9 is you need to get the surgeons or the whoevers to
 10 write less opioid for them going home. And
 11 clearly, as Bob was saying earlier, if we get to
 12 zero before they go home, then that's a clear
 13 demarcation point, but otherwise, you get 20 pills
 14 and use 10, and you still have 10 in the cabinet.
 15 DR. STACEY: I would say yes, which is -- I
 16 don't think Dr. Loeser would mind me telling this
 17 story because I'm sure he's shared it with several
 18 of you in the room. He had surgery. This is John
 19 D. Loeser, had surgery, a relatively minor -- not a
 20 big deal surgery. He received 120 tablets of a
 21 medication and used a handful of them, or less than
 22 a handful of them. So he had a whole bunch sitting

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1 around.
 2 If instead he had been prescribed 15, that
 3 would make a big difference. If this person at the
 4 beginning of the story, his family had been
 5 prescribed 5 or 10 per episode, would not have been
 6 able to come up with dozens, and may not have come
 7 up with a dose that would have been potentially
 8 fatal.
 9 So I think dose reduction in the unmonitored
 10 setting of not in the hospital is what really
 11 counts for reducing overdose tests. Because how
 12 many of you have done opioid trial? Raise your
 13 hand if you've participated in a trial of an
 14 opioid.
 15 (Hands raised.)
 16 DR. STACEY: How many of you have had an
 17 overdose death in that trial?
 18 (No hands raised.)
 19 DR. STACEY: Oh, so clinical trials never
 20 kill somebody. Drugs must be all safe if no one
 21 ever dies in the trial. Right? That's not true.
 22 So we need to do some extraction to the real world.

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1 DR. FARRAR: And I agree completely. My
 2 question, though, was not about writing less
 3 opioid. That doesn't strike me as opioid sparing.
 4 What that is a procedural process where we don't
 5 give too much opioid to people going home. When
 6 we're talking about opioid sparing, we're talking
 7 about reducing the amount that people take.
 8 DR. STACEY: So the reason that John was
 9 able to go home is he got multimodal analgesia, and
 10 he had an effective multicomponent analgesic
 11 approach that led him to be able to take less
 12 opioids.
 13 DR. FARRAR: But he went home with 120, and
 14 that's the issue that ultimately led to the death
 15 of the -- or the near death of the patient you were
 16 describing.
 17 DR. STACEY: So I think the way to think
 18 about it is that we need to -- if we're part of the
 19 perioperative experience, we need to look beyond
 20 the discharge and think about I want to get the
 21 maximum for benefit for what I do that extends
 22 beyond. So there's that. And then also when we're

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1 doing refills in the chronic pain situation, think
 2 about chronic pain medications; think about that,
 3 too.
 4 So that's not clinical trial stuff. That's
 5 not clinical trial stuff. If you reduce the need
 6 for the opioid, you can prescribe less, and the two
 7 have to go together. There's been a disconnect,
 8 now, with this, which there are various protocols
 9 that reduce the pain, reduce the drive, yet the
 10 prescription still stays up here. So that's less
 11 meaningful than if it's combined with the second
 12 part.
 13 DR. RATHMELL: Just one more question.
 14 DR. GROL-PROKOPCZYK: Hanna Grol-Prokopczyk,
 15 University of Buffalo. I'm still thinking about
 16 what opioid sparing means, as it seems most of us
 17 are. And now I'm thinking it's not just that one
 18 component or one parallel concept is reducing
 19 adverse effects. But based on your comment,
 20 there's reducing the dosage that people actually
 21 take and ingest, and then there's reducing the
 22 dosage that's prescribed. And the additive

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1 difference between those two is what's leading to
 2 the pills in the cabinet that people can get.
 3 So maybe it's worth thinking about -- I
 4 don't know if a clinical trial is designed to
 5 address the amount of prescribed independent of the
 6 amount used, but that's something as a health
 7 policy issue should be addressed.
 8 DR. RATHMELL: What we've seen is dozens and
 9 dozens and dozens of trials in an incredibly short
 10 period of time trying to define how many pills do
 11 you need after X, Y, or Z surgery. And that's
 12 actually happened. That's happened wholesale
 13 across the United States, is a reduction in
 14 prescribed, tailored much closer to what patients
 15 actually need for a given procedure.
 16 DR. STACEY: All within the last 5 years.
 17 DR. RATHMELL: Yeah, very, very short
 18 timeframe where all that's come out. And it's the
 19 surgical colleagues that have done most of that
 20 work.
 21 Thank you, Brett.
 22 DR. STACEY: Thanks.

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1 (Applause.)
 2 DR. RATHMELL: Next is Srinivasa Raja.
 3 Dr. Raja is a professor of anesthesiology in
 4 neurology and director of pain research at Johns
 5 Hopkins. And he's going to talk to us today about
 6 sparing of opioid related patient-reported side
 7 effects and symptoms.
 8 Thanks, Srini.
 9 Presentation - Srinivasa Raja
 10 DR. RAJA: Thank you, Jim.
 11 I see a little bit of that puzzled
 12 expression in Bob and Dennis' face because the
 13 title isn't exactly the same as what is in the
 14 agenda. There are two reasons for this, and two
 15 challenges that I faced. One was when you speak
 16 later in the afternoon, how do you come up with a
 17 presentation that doesn't duplicate what's been
 18 already said by these excellent speakers in the
 19 morning? The second challenge was after about four
 20 weeks of trying to prepare for this talk, I found
 21 myself challenged in trying to spend the next 30
 22 minutes sounding semi-intelligent to this erudite

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1 audience.
 2 So what I did was what my colleague Eric
 3 Strain did this morning, which is ask for some help
 4 from Mr. Google. So when I faced this challenge
 5 and asked Mr. Google what should I do under these
 6 conditions, the answer I got was, when you don't
 7 have a good answer to a question, change the
 8 question.
 9 (Laughter.)
 10 DR. RAJA: So that's some of what I'm going
 11 to be doing. The other, in defense of what Sharon
 12 was doing this morning in her presentation, she
 13 said she's going to be asking more questions rather
 14 than answering some of them, Google also defended
 15 her and had this advice. Asking the right question
 16 is often more important than giving the right
 17 answer. And this was defended by quoting Einstein,
 18 who said, "If I had an hour to solve a problem, I
 19 spend 55 minutes thinking about the problem and
 20 5 minutes thinking about the solutions."
 21 So what I'm gonna do in this presentation is
 22 be somewhat provocative, ask questions, use some

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1 reports in the literature, and try to provide some
 2 conceptual framework for this.
 3 In 1978, I was doing my anesthesiology
 4 residency, and the big news at the University of
 5 Washington, the big news was the Lasker Award being
 6 shared by Sol Snyder, Hans Kosterlitz, and John
 7 Hughes for opioid receptors and enkephalins, a
 8 discovery of the receptors and the endogenous
 9 opioids. So it is ironic that 4 decades later,
 10 we're looking at the adverse effects of drugs
 11 working on these receptors.
 12 We know that the receptors are ubiquitous.
 13 They are present in the central nervous system, the
 14 pulmonary system, the hepatobiliary system,
 15 cardiovascular, and endocrine systems, so it's not
 16 unusual or unexpected that there will be adverse
 17 effects. We're looking at the CNS effects, such as
 18 sites of brain or spinal cord for the analgesia,
 19 but we also know that the same CNS sites of
 20 actions, where opioid receptors are present, may
 21 also cause sedation, depression, change in
 22 cognition, and opioid-use disorder.

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1 The effects of these drugs at the other
2 systems, other sites, results in these variety of
3 adverse effects or off-target effects you can call
4 it, such as sexual dysfunction, nausea, vomiting,
5 constipation by the effects on the GI tract, immune
6 system changes resulting in immunosuppression and
7 infection; effects on the biliary tract causing
8 biliary obstruction, or respiratory depression due
9 to the effects on the CNS and pulmonary system, and
10 QT prolongation from cardiovascular effects.

11 Another way of looking at the same adverse
12 effect could be what are those opioid related
13 adverse effects due to? Are these due to receptors
14 at peripheral organs or is it due to sites on the
15 central nervous system. For example, CNS effects
16 could result in sedation, euphoria, or delirium.
17 They can also cause respiratory depression and
18 opioid-use disorders. And the peripheral sites of
19 action can result in gastrointestinal side effects,
20 genital urinary side effects, or endocrine side
21 effects.

22 So one way of potentially conceptually

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1 thinking is maybe what is the site of action, where
2 are the drugs working, and is it an adverse effects
3 related to the peripheral site of action or central
4 site of action.

5 We've already heard today that after
6 surgery, one has adverse effects, and this is just
7 one such example that maybe about 12 percent of
8 side effects related to respiration, GI, or GU, and
9 that this may be more in men versus women,
10 particularly after GI surgeries. Similar types of
11 incidence studies have shown that in chronic
12 non-cancer pain patients, Randy Moore or Henry
13 McQuay had this view, which looked at the adverse
14 effects of chronic opioids. And here it seems that
15 a little bit more of the GI effects and the CNS
16 effects may be more prominent.

17 A more recent analysis of multiple trials
18 show that the CNS effects of respiratory depression
19 may be less than 1 percent; falls and fractures may
20 be 1 to 2 percent. But what's more predominant
21 after chronic use are the hormonal effects, the
22 effects on sedation, sleep, and depression, which

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1 is more along the lines of 15 to 40 percent. So
2 depending on how the systems are, how the drug is
3 used, whether it be acute or whether for chronic
4 use, the relative incidence of adverse effects may
5 vary.

6 We've also heard that the adverse effects
7 result in economic burden. In this case, just an
8 example from post-surgical pain and giving just one
9 adverse effects, which is postoperative ileus, that
10 patients who got opioids or had ileus, the cost
11 went up, but doubled compared to those who did not
12 have it.

13 Another way of looking at these adverse
14 effects is maybe looking at the temporal
15 relationship of when the drug was given and when
16 the adverse effect occurred. For example, opioids
17 given for acute pain, there are some immediate
18 effects, such as respiratory depression and CNS
19 sedation. This may occur within minutes to hours.
20 There may be some intermediate effects that may
21 occur over days, such as changes in immune function
22 resulting an infection or delirium resulting in

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1 delayed functional recovery, or the more delayed
2 effects such as susceptibility to opioid-use
3 disorder.

4 Depending on when these occur, your outcome
5 measures or metrics that you may use may change.
6 For example, for the immediate effects, you may
7 look at perioperative morbidity or mortality. If
8 it's an intermediate effect, you may look at
9 infection rates or progression of cancer in
10 patients with cancer. For the delayed effects,
11 you're more interested in the opioid-use disorder
12 incidence or drug related deaths.

13 The same scenario can be made for use of
14 opioids for chronic pain, and again can be thought
15 of as immediate, intermediate, or delayed effects.
16 And similarly, based on which effect you're looking
17 at, again, the metrics or the outcome measure may
18 be different. For example, for the intermediate,
19 you could look at infection rate or sexual
20 dysfunction or depression or suicide. For the
21 delayed effects, the incidence opioid-use disorders
22 or drug related deaths.

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1 The reason for that is the temporal
2 relationship of the adverse event to the opioid use
3 will dictate what should be the metrics that we
4 use. It should be direct measures. Are they more
5 surrogate measures? What are the sources of data
6 that you may want to look at to examine these
7 adverse effects and what type of data you would
8 use. It will give you an estimate of what is the
9 frequency of the event, and therefore what are the
10 number of patients that you may have to recruit and
11 when you collect the data.

12 I happen to, in this case, agree with Bob
13 that I thought we would not have these 50-plus
14 experts sitting in one field if the delayed
15 effects, the opioid-use disorders and mortality,
16 were the primary. So I'm going to focus my
17 presentation a bit more towards those two adverse
18 effects.

19 We've already heard from Eric this morning,
20 and we are all familiar with the data on the
21 increased use of opioids and the increased
22 mortality. But what I did was a PubMed search on

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1 opioid sparing and pain over the last decade and
2 found this interesting graph, which shows that over
3 the last 4 or 5 years, there's a dramatic increase
4 in the number of publications, which have the term
5 "opioid sparing."

6 So then I asked the question what prompted
7 this increase in reports in the literature of
8 opioid sparing? I came up with this assumption
9 that opioid use associated adverse effects and
10 deaths are dose related; that opioid sparing can
11 reduce opioid adverse effects, which in turn may
12 reduce the opioid-use disorder and maybe opioid
13 related deaths.

14 So the questions I then tried to answer,
15 looking at the literature, were it is the evidence
16 of relationships between dose and adverse effects;
17 what strategies can be used or can help us assess
18 if opioid sparing will result in decrease in the
19 adverse effects, particularly opioid-use disorders
20 and opioid related deaths; and how do we determine
21 what is meaningful sparing of opioids that could
22 lead to a clinical decrease in adverse effects?

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1 So what I'm gonna do in the next few slides
2 is present some reports in the literature and see
3 whether we can determine this relationship between
4 opioid sparing and opioid adverse effects if it is
5 dose related. And if so, does that result in
6 reduction in opioid-use disorder and opioid deaths.

7 Let's start with this study, which just
8 looked at all patients admitted to the hospital in
9 a Denver academic center, over 6,600 patients.
10 And they looked at patients who were described as
11 opioid naive based on not having any prescriptions
12 for opioids in the year before the admission. So
13 prior to their hospitalization, they had not used
14 opioids at least for 12 months, and then looked at
15 over the next year how many of these patients were
16 using opioids.

17 They had two groups; 25 percent of the
18 patients got a prescription of opioids when they
19 were discharged; 75 percent did not get a
20 prescription for opioids. And the majority, as you
21 can suspect, the patients who got the opioids were
22 surgical patients, about two-thirds of them, and

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1 some of them had chronic pain. And then when they
2 looked at the use of opioids, a year later, chronic
3 opioid use in the patients who got a prescription
4 for opioids at the time of discharge had an odds
5 ratio of being more than 3 times likely that in the
6 next year they'll continue to have a script. So at
7 least they would have received a script for opioids
8 one year after the discharge.

9 The other thing they looked at this is, was
10 there a difference between those who were
11 discharged after a surgical admission versus a
12 nonsurgical admission, and they found that in
13 patients who were admitted for nonsurgical
14 indications, the odds ratio is almost double that
15 for surgical admission. So I think here is an
16 opportunity where we have a less well studied,
17 high-risk group of patients to look at. So
18 patients admitted to the hospital for nonsurgical
19 indications may even be a higher risk than surgical
20 indications.

21 There are limitations of this kind of
22 studies. These are retrospective cohort studies.

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1 It looks at opioid prescriptions, in this case from
2 a single pharmacy that these patients are sent to.
3 All that we know is they got a prescription. We
4 don't know how they used it, whether this is an
5 opioid-use disorder, did they misuse a
6 prescription, did they abuse it, did they divert
7 it. We don't know that from this particular study.
8 So we have a lot of studies that are in the
9 literature in recent years that have focused on
10 postoperative patients and what happens in
11 opioid-naive patients when they are discharged.
12 Here are two studies, one of which was shown by TJ
13 Gan this morning. The one from the left is from
14 Stanford, the right is from Michigan. And again,
15 they looked at large databases, in one case or
16 600,000 patients undergoing surgery over a 2-year
17 period, and the other about 36,000 patients. They
18 said opioid naive means no prescription for opioids
19 in a 12-month period prior to surgery. Then they
20 looked at 12 months post surgery, looking at what
21 they defined as chronic opioid use.
22 This was a variety of surgical indications.

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1 The Stanford group said there were 0.5 percent
2 ranging from .12 to 1.4 percent. On average, about
3 0.5 percent were considered as chronic opioid use.
4 The Michigan group said it was 5.9 to 6.5 percent.
5 So again, we can see there's a tenfold difference
6 between these two studies. And what causes this
7 tenfold difference?
8 The answer I think is, is what is the
9 outcome measure that these two studies used? The
10 first question, you can say that maybe the
11 incidences are different because the type of
12 surgery is very different in these cases. I then
13 took two identical surgeries, laparoscopic
14 appendectomy, laparoscopic cholecystectomy, which
15 were in both groups. And again, if you look at the
16 data, there was a 15 to 25-fold difference between
17 the incidence of chronic opioid use between these
18 two studies.
19 So what's the difference? The difference is
20 this. In the right study in Michigan, they said
21 any opioid prescription, 90 days to 180 days after
22 surgery meant chronic opioid use. If they had a

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1 prescription within 90 to 180 days after the
2 surgery, that was chronic opioid use. The left one
3 was much more conservative, and they said 120 days
4 supply in the 90 to 12-month period or greater than
5 10 scripts during the 1-year period. So you can
6 see these two outcome measures are very different,
7 resulting in very different proportion of patients
8 who are considered chronic opioid users.
9 The questions that you can ask and came to
10 my mind as well is which outcome measure is more
11 reflective of opioid-use disorder? Filling the
12 prescription, does that mean they are misusing,
13 abusing, or diverting the opioids? Is there any
14 relationship to the postoperative opioid dose that
15 these patients were given, the scripts that they
16 were given? And these were not studied in this or
17 if they were studied [indiscernible]. And is
18 opioid sparing likely to change this incidence? So
19 do we have any data based on that?
20 Just about a week ago, I came across this
21 study that was from actually the Harvard group. It
22 was published in BMJ. And they looked at a large

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1 database, the Aetna database consisting of
2 37.6 million patients. And about a million of
3 those patients had surgery over a 8-year period,
4 2008 to '16. And they used CPT codes to indicate
5 that these patients had surgery.
6 In those million patients, they also looked
7 for ICD codes for opioid dependence, opioid abuse,
8 or overdose. They picked up a number of ICD codes,
9 which will be reflective of dependence abuser or
10 overdose. And they observed that 57,00 had
11 received postoperative opioids. So 56 percent of
12 these patients who had surgery had postoperative
13 opioids. And of those, close to 6,000 had an abuse
14 code in the subsequent period.
15 What that says is what one could think of as
16 0.6 percent of all surgical patients had an abuse
17 code or maybe 1 percent of those who received
18 opioids had an abuse code. This was about a
19 2.7 year after their surgery. They also looked at
20 a variety of things. It was over an 8-year period,
21 and they found that males, particularly in the 15
22 to 24 age group, had a higher incidence of this

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1 misuse diagnosis.

2 The next question that's the most important

3 question and the most relevant question for our

4 discussion is, is there an association between this

5 misuse and the dosage that was prescribed to these

6 patients? When they looked across the dosages, the

7 slope of that line is fairly flat. Although there

8 is some correlation, it says that an increment of

9 10 morphine equivalence only increases the hazard

10 by about 0.8 percent. So the relationship between

11 dose increments and the misuse diagnosis was fairly

12 weak.

13 So reducing dose of opioids in the

14 prescription, daily doses of opioids, may have a

15 weak effect on lowering opioid-use disorder. So

16 the question is, is there some other relevant,

17 useful indicators? And obviously, I wouldn't be

18 presenting this paper unless I thought there was

19 something relevant, and that is this. If they

20 looked at the correlation, the slope, it's a much

21 better slope of the duration of the initial use

22 after this surgery in terms of the misuse rate.

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1 What this suggests is that the duration of

2 prescription rather than the dosage is much more

3 strongly associated with the ultimate diagnosis of

4 misuse. Obviously again, this is administrative

5 data, so that's a limitation. One could say this

6 is an underestimate because maybe the miscoding of

7 abuse may be an underestimation. And opioid use,

8 this is, again, scripts that were filled, and that

9 doesn't mean were they using it appropriately and

10 what happened; is this misuse, abuse, or diversion?

11 Until recently, a week ago, I was an

12 optimist. I felt a good, well orchestrated

13 preoperative opioid-sparing strategy will have a

14 major effect on the opioid crisis. However, I'm

15 starting to feel more pessimistic, and I think the

16 problem is much more challenging and complex than

17 what we think is.

18 Why do I say that? I'll give you a couple

19 of examples of why I think this is more complex.

20 Here again, we heard from a couple of speakers

21 talking about postoperative or perioperative use of

22 opioids and how the ERAS or enhanced recovery

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1 program may be a good way of opioid sparing.

2 Here is an excellent study from the UCLA

3 group. They looked at a 12-month period when they

4 initiated the ERAS program. And you can see in the

5 left half, they've shown a dramatic reduction in

6 the perioperative use of opioids, which are

7 persisted in the next 12-month period. So this is

8 kind of the introduction of the program and the

9 subsequent program.

10 Then they looked at what happened to these

11 patients when they were discharged home, and the

12 prescription of the opioids were fairly similar

13 across the 24-month period, again, reemphasizing

14 opioid prescription at hospital discharge may have

15 no relationship to what happened in the

16 interoperative period. So opioid sparing in

17 hospital may not decrease opioid prescriptions at

18 discharge.

19 Another cause for pessimism for me was,

20 again, the Brat study from the Harvard group, which

21 looked at a number of different specialties and

22 their behavior over the course of the next several

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1 years. And you can see trends, a number of

2 specialties such as general surgery had decreasing

3 opioid use post-surgery in the several year period.

4 But when you look at the right in terms of

5 relationship between the duration of use and the

6 misuse diagnosis, that remained constant.

7 There doesn't seem to be a

8 significant -- although the prescription opioid

9 decreased, it didn't seem to reflect in the

10 relationship between duration of use and the misuse

11 diagnosis, again suggesting that maybe just the

12 dose of opioid that they were discharge with is not

13 the most important factor.

14 So despite mean opioid dose reduction -- and

15 the dose reduction varied from 4 to 24 percent;

16 even 20 percent reduction, there was no

17 relationship or change in relationship between that

18 and misuse. So again, you can say that the ICD

19 code is underestimation, and maybe patient-reported

20 outcome measures are more important.

21 We shouldn't be surprised with this because

22 when you look at PK levels, the dose of oxycodone

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1 correlates very well. It's in 20, 40 and 80
2 milligrams. The peak plasma concentrations are
3 linear. But when we look at things like drug
4 liking behavior, there is a saturation effect. It
5 seems like between 20 and 40, there is a change,
6 but between 40 and 80, the liking behavior doesn't
7 change.

8 So the question you can ask as if I reduce
9 or spare the opioid from 80 milligrams a day to 40
10 milligrams a day of oxycodone, am I going to change
11 the opioid-use behavior in the perioperative period
12 or in chronic use? So this again raises the
13 question, what dose is required to change this
14 liking behavior associated with opioids? And we
15 don't know the answer for that. It's definitely
16 not a linear relationship.

17 So there are a number of patient-reported
18 safety measures of opioids: abused safety efficacy,
19 a nice review. Nine of these instruments are being
20 studied. Some of them look at the global effect of
21 safety, efficacy, and misuse, some a single measure
22 of constipation; others of just misuse.

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1 So depending on what you're focusing on, a
2 number of these measures that are available.
3 Unfortunately, this review concluded that the
4 clinical utility of these measures are equivocal,
5 that some of these measures are not really feasible
6 in clinical practice because they are either too
7 long or too challenging. Some of them require
8 trained observers and need to be further validated
9 measures.

10 There are some measures available, which
11 look at risk of aberrant behaviors, but if you're
12 looking at the intent of the aberrant behavior,
13 whether it is misuse, abuse, or diversion, there
14 are only two measures that I'm aware of that
15 specifically looks at that. And this was a focus
16 of one of the ACTTION meetings in 2013. It took
17 about four years for that paper to come out. It
18 was published by Shannon as the first author last
19 year. And they compared two main measures, the
20 self-reported misuse, abuse, and diversion
21 instrument, or SR-MADs, and MADDERS, which is the
22 other measure, which Nat Katz was much involved in.

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1 There are differences between these
2 measures. Again, SR-MAD is a 15-item measure,
3 self-reported, used primarily for prospective use.
4 And it maintains the anonymity of the patient and
5 is also easy to use. It has some content
6 validation in terms of patients with chronic pain.
7 It's a qualitative study. But the construct and
8 the predictive validity have not been done..

9 In contrast, MADDERS can be used
10 prospectively as well as retrospectively. It is a
11 little complex in the sense it's triggered by
12 either self-report of adverse events or by drug
13 accountability discrepancies, followed by an
14 interview of intent, and then additional data
15 that's available during the clinical trial.

16 So it depends on which context you're going
17 to be using this. If you're using it in
18 large-scale studies which may be needed for
19 opioid-use disorders or opioid related deaths
20 because of the small incidence of those, then you
21 may have to use a scale that's easy to use.
22 However, in the context of smaller clinical trials,

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1 MADDERS might be much more practical or usable. So
2 I think these two measures still need further
3 validation in terms of their sensitivity and
4 specificity, but what measure you use will depend
5 on the context of the study.

6 The last couple of slides, if you think
7 opioid-use disorders was challenging, how about
8 deaths related to opioids? The first study, this
9 kind of dose related event of death and chronic
10 pain patients using opioids came from the VA health
11 data, which categorized patients on chronic opioids
12 into buckets of no opioids, 1 to 20 milligrams; 20
13 to 50; 50 to 100; more than 100 in a broad group of
14 patients, different categories.

15 They said whether it be a chronic non-cancer
16 pain patient, a cancer diagnosis, or acute pain
17 diagnosis, overdose related deaths was dose
18 related. For example, for chronic non-cancer pain,
19 if you use 1 to 20 milligrams, the death rate per
20 100,000-person months was .11 and 20 to 50 was .24.

21 So it gives you a little bit of what should
22 be your sample size to be able to show differences,

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1 but this uses buckets, which are fairly broad, 20,
2 30, 50-milligram differences. So the question is,
3 what is going to be important?
4 The same group, because they were unhappy
5 with categorizing these patients into buckets, they
6 then did a subsequent study where they had a nested
7 case control with matching, looking at patients who
8 died and patients who didn't die with different
9 opioids. And they did find patients died after
10 chronic opioids at a higher dose, but they could
11 not determine a clear-cut point in the opioid
12 dosage to distinguish between those who had
13 overdose cases or those who died of overdose and
14 the controls. So we don't have a clear-cut point
15 of where there's a differentiation.
16 Then the lowering of recommended dosage,
17 what they concluded was if they lowered it less
18 than 100 morphine equivalence, it only affected a
19 few patients that were not at risk, but maybe many
20 patients were at risk. So that tells us that you
21 may be wanting to -- if you're going to design a
22 study, you may need to include those patients at

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1 higher risk and not ignore those patients.
2 Finally, anesthesiologists using these ERAS
3 programs have said that we have an old way of
4 treating patients in the perioperative period,
5 where opioids were at the bottom of this pyramid,
6 and now they should move up to the top of the
7 permit. I think this is one way of looking at it.
8 But I rather think that this should be actually a
9 team effort where it's not just the
10 anesthesiologists, but a whole group of individuals
11 working to determine not just perioperative
12 immediate use, but the longer-term use.
13 To conclude, the points I would like to make
14 is in acute pain management, the acute adverse
15 effects, the immediate effects, may be dose
16 related. And in those cases, opioid sparing may be
17 beneficial. But perioperative opioid sparing just
18 in the immediate perioperative period does not
19 necessarily equate to lower prescription at
20 discharge, and that needs to be looked at as well.
21 In chronic opioid use in opioid-naive
22 patients, we need to focus on how long these

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1 opioids are used; that is the duration of therapy
2 post-surgery is important more than the dose of the
3 opioid, that the patient-reported measures to
4 detect misuse, abuse, and related events need
5 further validation to test their sensitivity and
6 specificity. And we have little quantitative data
7 at this stage as to how much of a reduction in
8 opioid dose will lead to a meaningful reduction in
9 opioid-use disorder or in death. Thank you very
10 much.
11 (Applause.)
12 MALE VOICE: Thank you. You've made us all
13 pessimists.
14 DR. RATHMELL: We're all pessimists now.
15 Okay, let's go home.
16 We're a bit over time. I'm going to respect
17 the break. There will be plenty of time at the
18 end. We're going to have all of the panelists for
19 an hour at the end, so there's plenty of time for
20 questions. I know you probably all have them. So
21 back here promptly at half past the hour.
22 (Whereupon, at 3:05 p.m., a recess was

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1 taken.)
2 DR. RATHMELL: We'll go ahead and get
3 started again.
4 Next on the docket, Dr. Ward, Denham Ward.
5 He's professor emeritus in the Department of
6 Anesthesiology and Biomedical Engineering at the
7 University of Rochester, and he's going to talk to
8 us today about opioid sparing relative to
9 respiratory depression.
10 Denim, thanks.
11 Presentation - Denham Ward
12 DR. WARD: We've heard a little bit about
13 respiratory in passing, so now I'm going to focus
14 on the respiratory. I'm a big believer in
15 experiential education, if you're going to remember
16 things. So we're going to start out with a couple
17 of little experiments here. This isn't a contest,
18 but I want all of you to put your hands up. Take a
19 deep breath out and hold as long as you can. When
20 you have to breathe in, put your hand down.
21 (Audience participation.)
22 DR. WARD: A lot of type A people here.

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1 Okay. That was a little demonstration of
 2 the voluntary control of breathing and the
 3 chemosensitive control breathing. You have
 4 voluntary control over your breathing to a certain
 5 extent, and then your autonomic chemoreceptors are
 6 going to kick in and say, "I don't care if you
 7 don't want to breathe; you're going to breathe."
 8 So it was two parts of the respiratory
 9 system that you just demonstrated. And I want to
 10 demonstrate a third part that's probably a little
 11 bit better exercise than the first one. I want
 12 everybody to close your eyes, take a slow deep
 13 breath in, hold it for just a second, and then take
 14 a slow, deep breath out. And when you finished
 15 exhaling, open your eyes.
 16 (Audience participation.)
 17 DR. WARD: So now that you all feel more
 18 relaxed after that little breathing exercise, you
 19 see a connection between your breathing and your
 20 limbic system; how your breathing can actually
 21 affect how you feel. So the brain has a lot of
 22 effects on breathing through a variety of systems.

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1 Quick disclosures, I do some consulting with
 2 some drug companies once in a while. What I'm
 3 going to try to cover initially is how we measure
 4 respiratory depression by opioids, both in the
 5 laboratory where we measure end-tidal CO2 and
 6 decrease in ventilation in the hypercapnic
 7 ventilatory response, HCVR, and the hypoxic
 8 ventilatory response, HVR, and clinically how we
 9 perhaps use saturation end-tidal CO2 and
 10 ventilatory arrhythmias; but then some
 11 complications on how we would develop study designs
 12 that include things like sedation, sleep, and
 13 concurrent pain that may affect our breathing.
 14 Then I want to go through some examples, and
 15 I've divided it up into opioid sparing, in spite of
 16 all the discussion we've had about what really is
 17 opioid sparing, and opioids plus peripheral
 18 analgesics such as the NSAIDs; opioids plus central
 19 sedatives, traditionally like the central
 20 antipsychotics, anti-nausea vomiting medicines; and
 21 opioids in the new central analgesics, things like
 22 dexmedetomidine, pregabalin, and ketamine. And

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1 finally, I'm going to throw out some
 2 recommendations, I guess with my recommendations
 3 for recommendations so it can be then modified by
 4 the group.
 5 Fred Plum I think had one of the best
 6 definitions talking about breathing being
 7 independently controlled. Breathing is the only
 8 coordinated skeletal muscle act that continuously
 9 fulfills, seamlessly integrates continuous
 10 metabolic and intermittent behavioral functions
 11 without normally disrupting the efficiency of
 12 either in the process; exactly what I'm doing right
 13 now. I'm breathing and talking -- besides talking
 14 and chewing gum at the same time, I manage to
 15 breathe and talk at the same time. And if you
 16 measure my arterial CO2, it would actually be
 17 normal. I'm able to integrate voluntary and
 18 involuntary seamlessly.
 19 Traditionally, back in medical school, we
 20 were probably taught things like the
 21 chemoreceptors. We were taught that there were
 22 brainstem respiratory centers in the medulla and

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1 pons, and they went down the phrenic nerve to the
 2 diaphragm that controlled the lung function. And
 3 then there were central chemoreceptors and carotid
 4 bodies that measure the PCO2 and measure the PO2.
 5 And then on the right-hand side, upper panel there,
 6 you can see if you increase the CO2, you get a
 7 pretty linear increase in ventilation, a typical
 8 slope of 2.5 milliliters per minute per millimeter
 9 of mercury of CO2.
 10 So if you end up with a CO2 of about 50,
 11 ventilation is up to around 30. I can point it out
 12 here, but not everyone in the back can see the
 13 pointer, and it's hard from this angle. But a CO2
 14 of 50 ends up with a ventilation of about 35 or 40
 15 liters a minute, about 4 or 5 times normal.
 16 We sometimes see patients in the recovery
 17 room, recovering from anesthesia with a CO2 of 50,
 18 and we don't really think too much of that. But if
 19 I give any of you a CO2 of 50 millimeters of
 20 mercury to breathe, you're going to be breathing at
 21 about 40 liters a minute. Similarly, with
 22 desaturation, which is a linear decrease with the

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1 saturation -- the lower panel there shows it with a
2 desaturation of about 80 percent -- the ventilation
3 is up around 20, 15 or 20 liters a minute. Those
4 are both graphs from my lab from individual
5 volunteers.
6 But it's really more complex than that.
7 It's not just that nice little -- as we
8 demonstrated with our little exercises that we did,
9 the chemoreceptors is only part of the whole
10 control of breathing. We really have to take into
11 account the cortex. The subcortical limbic system
12 has a lot of effect on it, and then not just the
13 chest wall with the upper airway obstructions, too,
14 with really a much more coordinated system that the
15 opioids are going to act upon than just that simple
16 metabolic CO2 controller.
17 Functionally, it's much better to think
18 about dividing a system up more like this, as
19 3 pathways that control our breathing. There's the
20 traditional metabolic control. There's a CO2, O2
21 chemoreceptors, the carotid bodies, and the central
22 medulla. But there's also a wakefulness drive.

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1 There's a behavioral control. Pain may come
2 through that pathway. And there's a voluntary
3 control. You can breathe. You can take a deep
4 breath when and where you want to.
5 Normal resting is really a mixture of all
6 three of these/ In different states, there are
7 different effects. Normally resting, the first row
8 there, probably is controlled mainly by behavioral
9 and not CO2; maybe a little bit from CO2 and a
10 little bit from voluntary, depending on what you're
11 doing at the time.
12 Anaerobic exercise where you're generating a
13 lot of hydrogen ion is clearly a metabolic control.
14 For those of you who jog or run, once you get to
15 about 20 liters a minute, you find you can't talk
16 to the person that you're running beside because
17 voluntary control is not going to be effective when
18 that metabolic control from exercise has kicked in
19 REM sleep looks like more behavioral.
20 There's actually not much response to CO2 on the
21 REM sleep; REM sleep looks more like awake, as
22 opposed to non-REM sleep, when you don't have,

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1 obviously, any voluntary control, the behavioral
2 limbic system is suppressed by the non-REM sleep,
3 and you're pretty much just under metabolic
4 control.
5 Singing, talking, arousal, things like
6 Ondine's curse and locked-in syndrome have their
7 own effects. But what do opioids do? Opioids
8 pretty much suppress metabolic control. Depending
9 on the amount of sedation, it will suppress the
10 wakefulness control. And it leaves the voluntary
11 control more or less intact. Those of us who are
12 anesthesiologists have often given a fair amount of
13 opioid to a patient, so they've stopped breathing,
14 and then just asked them to take a deep breath, and
15 they surely will take a nice deep breath, a deep
16 breath for us. The voluntary control will still be
17 intact.
18 The one that surprises people, which I'm not
19 quite sure why it should, because this was shown by
20 Ray Fink many, many years ago, is the fact that
21 normal resting ventilation is not really controlled
22 by CO2. That still seems to be the dogma that's

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1 being taught most frequently. And what Ray did at
2 Columbia in the early '60s, we took a group of
3 volunteers who weren't physiologists and didn't
4 really know that CO2 controlled breathing, and
5 asked them to hyperventilate. And they
6 hyperventilated down to CO2's in the low 20's, and
7 then just said, okay, just breathe.
8 Now, if I asked you to do it, you'd probably
9 stop breathing because you know if your CO2's only
10 20, you're not going to have any drive to breathe.
11 None of these volunteers did. Their breathing kept
12 right on at the level that it was. So here's the
13 CO2. They hyperventilated themselves down to here.
14 Here's after they stopped hyperventilating, and you
15 see actually it was still up a little bit, and then
16 stayed put. There was apneic period there.
17 So as Ray said, "Cerebral activity
18 associated with wakefulness probably plays an
19 important role in the maintenance of resting
20 respiratory rhythm. Carbon dioxide appears to play
21 a subsidiary part, and the main respiratory drive
22 appears to be of neural origin."

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1 Well, how about opioids? We've been talking
 2 about opioids and its effect on nausea, vomiting,
 3 constipation, all these other effects. Well, it
 4 also has a strong effect on breathing and one which
 5 we can quantify quite readily; a lot of different
 6 studies dating back to the 1940's. Santiago in
 7 1979 had a nice paper because he combined the
 8 effects on both the hypoxic and hypercapnic
 9 effects, actually as well as exercise in the paper,
 10 too; 0.2 milligrams per kilo of morphine IM, a
 11 reasonable dose; ventilation decreased from 6.8
 12 liters a minute to 5.1, with a decrease in both
 13 tidal volume and respiratory rate.

14 The lower left-hand panel there shows the
 15 hypercapnic response. So again, you can see as the
 16 CO2 was increased, ventilation went up a slope of
 17 3.5 versus 1.8. It's probably more interesting to
 18 look at the ventilation at a CO2 of 50. So if you
 19 look at the upper curve at a CO2 of 50, the
 20 ventilation was about 50 liters a minute in this
 21 group of subjects. After morphine, the ventilation
 22 was about 20 liters a minute; so cut the

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1 ventilation by over half at a CO2 of 50.

2 A similar effect with the hypoxic response
 3 on the right-hand side, you can see the increasing
 4 ventilation with the decreasing saturation, a
 5 normal response about half a liter a minute per
 6 1 percent decrease in saturation. That was cut
 7 down to 0.16. And his example, it's also nice to
 8 look at what the ventilation would be at a
 9 saturation of say 70, which in the control was
 10 about 25 liters a minute. Oxygen is not as strong
 11 a stimulus to ventilation as CO2.

12 The combination is very strong. The
 13 asphyxial response of hypercapnia and hypoxia is
 14 the strongest response across. With a saturation
 15 of 70, ventilation went down from about 25 liters a
 16 minute, down to about 10 liters a minute; so a
 17 strong depression in both the hypoxic and
 18 hypercapnic response, more than what you would see
 19 at the resting level, I think what we would call a
 20 moderate dose of intramuscular morphine.

21 I can't talk about effects of opioids on
 22 respiration without the classic study by my mentor,

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1 Jay Bellville, who was my mentor at UCLA, who
 2 looked at the effects of sleep plus morphine. Most
 3 of the studies that are done, you've got a subject
 4 awake, maybe a mouthpiece in their mouth, breathing
 5 on an apparatus, and you give them some morphine,
 6 and they're still awake.

7 What happens if they fall asleep? In a
 8 study in Anesthesiology with 4 subjects, that would
 9 never get published today, of course, showed a
 10 drastic reduction in both the slope and the
 11 absolute ventilation, compared to rest, compared to
 12 morphine, compared to morphine plus sleep. So
 13 curve over in the right-hand side of the
 14 hypercapnic response curves, the steeper one is
 15 actually the morphine one and the flattened one is
 16 morphine plus sleep for one individual subject.
 17 And if you care, you can see the 4 individual
 18 subjects, the data.

19 As Jay said, "How much of the very
 20 substantial respiratory depression seen during
 21 anesthesia is related to the altered state of
 22 consciousness and how much is due to the drug

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1 per se?" Certainly this study poses many problems
 2 concerning the interaction of sleep, altered state
 3 of consciousness, and drug effects, because it's
 4 very difficult to associate out how much is just
 5 the drug itself that may be acting on the
 6 chemoreceptors and how much is acting on the
 7 cortical limbic systems by changing the mood,
 8 changing the affect, changing sleep, and changing
 9 sleep state. This study has only been reproduced
 10 once by, by Dick Neal, and that was about 25 years
 11 ago, finding the same thing. I'm not aware of it
 12 ever being done looking at REM versus non-REM sleep
 13 with opioids.

14 Now, I want to go through some examples.
 15 This is not a systematic review. It's not a
 16 scoping review. I just pulled out some papers that
 17 I thought had interesting methodology that were
 18 typical of the kind of methodology of the studies
 19 in these three areas: opioids plus peripheral,
 20 opioids plus central sedatives, and opioids plus
 21 central analgesics. And I've tried to divide them
 22 up both in volunteer studies that are done in the

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1 laboratory with perhaps a little more care about
2 the data that's being collected on the respiration
3 and clinical studies, mainly post-op acute pain
4 type studies.
5 Moren back in 1997 looked at an NSAID on a
6 double-blind, randomized crossover study, looked at
7 ketoprofen, morphine, and then the combination of
8 the two of them. Now, one thing commonly you see
9 in these studies is the combination uses the same
10 dose that they started out with the individual
11 ones, so you've got some potentiation there, or
12 not, but there's no effort to try to reduce the
13 doses to get equal analgesic. And in fact, almost
14 none of the laboratory studies have a good measure,
15 if any, of any kind of analgesic effect.
16 Interestingly, they did measure the
17 hypercapnic ventilatory response, and you can see
18 on the graph there, the open circles is the NSAID,
19 the slope. The close circles is the morphine, and
20 the open squares is the combination. So they
21 actually found the combination had less respiratory
22 depression than morphine by themselves, indicating

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1 that the NSAID partially reversed the respiratory
2 depression from morphine; an interesting result,
3 not really duplicated in many of the other studies.
4 They didn't do any analgesic effects.
5 Liu 1993, a lot of these are older studies
6 because we did these studies when these drugs first
7 came out often, and then kind of lost interest in
8 what their respiratory, morphine-sparing effects
9 would be. Liu in 1993 looked at post-op patients,
10 double-blinded, placebo-controlled saline versus 60
11 milligrams of ketorolac given pre-op. So he gave
12 IM ketorolac pre-op, and then looked at how much
13 pain there was in the PACU by measuring the amount
14 of fentanyl that they used.
15 They did find that there was less fentanyl
16 used, and the patients reported less pain in the
17 PACU. But the only thing they measured was some
18 lung mechanics. They measured some FEV1's, one
19 which hadn't changed. They had no measurements of
20 any of the control of breathing effects, including
21 saturation and end-tidal CO2, or any of the simple
22 clinical measurements.

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1 There are a lot of case reports out there,
2 and they're interesting. To illustrate the
3 difficulties of the interactions, Jain and Shah
4 back in '93 had a case report of respiratory
5 depression following a combination of epidural,
6 buprenorphine, and intramuscular ketorolac. They
7 had a patient that had an epidural buprenorphine
8 that was still having some pain; gave IM ketorolac,
9 and the pain decreased, and they got a respiratory
10 depression.
11 Pain is a wonderful anecdote to opioid
12 respiratory depression. And if you take away the
13 pain with another modality, then you don't count on
14 the respiratory depression and you increase the
15 respiratory depression, because the classic one for
16 an anesthesiologist is the patient with a broken
17 leg in the ED that gets a bunch of morphine to
18 control the pain, you bring him in the operating
19 room and put a spinal, and the pain goes away and
20 they stop breathing because the respiratory
21 depression from the opioid plus pain was not
22 substantial. The respiratory depression from the

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1 opioid with no pain is very substantial.
2 So it becomes difficult -- if you're going
3 to measure respiratory depression, you have to very
4 carefully define the state of how much pain is
5 involved, are they awake, are they asleep, and how
6 much sedation is involved because these other
7 things have a very strong effect on the respiratory
8 system.
9 How about the central sedatives? When I was
10 an intern back -- I won't say -- but back in the
11 early '70s, mid-'70s, 50 of demoral -- horrible
12 drug -- 50 drug, 50 of phenergan, that's at least
13 as good as 100 of demerol.
14 Anybody else from my era remember that 50 of
15 demerol, 50 of phenergan? That was what every
16 post-op patient got. Well evidently, in the '70s,
17 we hadn't read the literature because Arthur Keats
18 back in 1960 looked at that -- and again, a paper
19 that would struggle to be published today, but
20 looked at both post-op patients and volunteers in
21 the laboratory.
22 The post-op patients were not blinded or

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1 randomized, but looked at demerol 50 and phenergan
 2 50, plus morphine, and in volunteers randomized
 3 looked at demerol 50 milligrams, demerol
 4 100 milligrams, and demerol plus 50 and phenergan
 5 plus 50, and looked at the hypercapnic ventilatory
 6 response, and didn't find any effect. There was no
 7 increase in the analgesia. There was no increase
 8 in the respiratory depression. But they were a lot
 9 sleepier.

10 So he concluded the addition of promethazine
 11 to meperidine did not increase respiratory the
 12 depression, didn't increase the analgesia either,
 13 but markedly increased the sedative effects. So
 14 the 50 plus 50 really was not accomplishing
 15 anything as far as opioid sparing was concerned.

16 Sometimes you want to look for things.
 17 Olson 1986, in volunteers not blinded gave morphine
 18 .15 milligrams per kilogram and then randomized
 19 chlorpromazine, prochlorperazine, 12.5 milligrams
 20 versus saline. The morphine decreased the
 21 hypercapnic ventilatory response by about 40
 22 percent and decreased the hypoxic ventilatory

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1 response by about 50 percent. That's the same data
 2 that we kind of saw in Santiago's study that I
 3 showed you before.

4 The prochlorperazine/chlorpromazine had no
 5 effect on the hypercapnic ventilatory response, but
 6 the hypoxic response was reversed. The hypoxic
 7 response was markedly increased almost back to the
 8 pre-morphine level. And that's known because the
 9 carotid bodies have a dopaminergic receptor in
 10 them, and plus the chlorpromazine is an
 11 anti-dopaminergic drug, so that increases the
 12 hypoxic response and counters the effect of
 13 morphine.

14 So if you're looking for a hypoxic response,
 15 the central sedative actually counters the
 16 depression of the hypoxic response. Again, he made
 17 no analgesic measurements, so he cannot make any
 18 statement about whether the chlorpromazine had any
 19 increase in the analgesia.

20 Probably the more interesting drugs today
 21 are the three central analgesics. Peter Bailey
 22 back in '91 looked at clonidine PO, morphine IM,

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1 and then the same doses of clonidine plus morphine
 2 and didn't find a whole lot of an effect. Look at
 3 the two curves down in the bottom. The left-hand
 4 curve is the slope and the right-hand curve is the
 5 ventilation at a CO2 of 50, which is probably the
 6 more interesting one to look at.

7 You see the clonidine in the top curve did
 8 cause some respiratory depression. The morphine
 9 caused some respiratory depression, and the two of
 10 them together were pretty much additive; so the
 11 amount of respiratory depression from each one of
 12 them, added together to get the bottom curve, which
 13 is the clonidine plus the morphine. So a little
 14 bit of respiratory depression with the clonidine
 15 and less change in the slope. The left-hand curve
 16 shows clonidine did not have much of a change in
 17 the slope -- that's the top curve -- but it did
 18 shift the curve over to right.

19 Lin, British Journal 2009, looks at dex.
 20 It's a clinical study, post-op, double-blind,
 21 randomized, looked at morphine and morphine plus
 22 dex via PCA, and showed a decrease in the amount of

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1 PCA morphine being used as a measure of the opioid
 2 sparing, significant even at the 1-hour level. And
 3 very typical of these studies -- and I could have
 4 found multiple ones -- was the quote, "There was no
 5 report of somnolence or respiratory depression in
 6 this study." The misspelling is mine, not his. If
 7 you don't look for it, you're not going to find it.
 8 Saying that there was no report or respiratory
 9 depression does not mean that there wasn't
 10 respiratory depression.

11 Mildh in 1998 looked at ketamine, again, in
 12 volunteers, double-blind, crossover, randomized,
 13 looking at fentanyl, 2 mgs per kilo, and fentanyl
 14 plus ketamine. Interestingly, if you look at the
 15 bottom curve there, the fentanyl plus ketamine is
 16 the upper curve and the fentanyl plus placebo is
 17 the bottom curve, and this is just the minute
 18 ventilation, the resting minute ventilation. And
 19 you can see the fentanyl reduced the resting minute
 20 ventilation from about 8 liters a minute down to
 21 4 liters a minute, and that was counteracted by
 22 ketamine. So the ventilation went down but didn't

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1 go down anywhere near as much, and was a
 2 significant difference.
 3 That was their main finding. But if you
 4 read the paper a little more carefully, there was a
 5 statement in there that pulse oximeter saturation
 6 decreased to 90 percent in both groups. So there
 7 was a decrease in saturation at rest, less than
 8 90 percent, which a lot of us would put at the
 9 criteria which you'd want to have some sort of
 10 intervention, supplemental oxygen, even in the
 11 Ketamine plus fentanyl group. So the ketamine,
 12 while it did reverse some of hypoventilation, CO2
 13 only went up to 6 as opposed to 10, it was still a
 14 decrease in saturation.
 15 I wanted to show this because they
 16 illustrate there's a lot of things you can look at
 17 as far as what respiratory depression is after
 18 these drugs, and there's no consensus on exactly
 19 the right one to look at. And from the laboratory
 20 studies like the hypoxic ventilatory response and
 21 hypercapnic ventilatory response, there's not solid
 22 data, okay, if you're hypercapnic, your ventilatory

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1 response is reduced by 50 percent; that puts you at
 2 high risk for respiratory depression when you use
 3 the drug clinically. That data does not does not
 4 exist. That's some hypothesis out there that
 5 that's true.
 6 Michelet, British Journal in 2007, post-
 7 thoracotomy, which is an interesting use of the
 8 combination randomized control trial, pure morphine
 9 PCA versus morphine plus ketamine PCA. The
 10 left-hand panel there shows the decrease in
 11 morphine use as less PCA. And then they used one
 12 of the better, I think, outcome measurements for
 13 respiration in a clinical study.
 14 They measure the amount of time with
 15 saturation less than 90 percent, also at
 16 95 percent, but I used the 90 percent as perhaps a
 17 more clinically relevant number. That's probably
 18 when the intern would get called by the nurse, when
 19 the saturation got down below the 90 percent, so at
 20 least the intern on call probably cares about this
 21 one.
 22 As you see in the left-hand panel, there was

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1 a decrease, which didn't become significant until
 2 the cumulative dose at 36 hours. But there was a
 3 substantial significant, both clinically and
 4 statistically significant decrease in the percent
 5 of time spent below 90 percent saturation in these
 6 post-thoracotomy patients. These are all
 7 lobectomies. They are open thoracotomies without
 8 any epidurals, so the amount of splinting and
 9 post-op pain is pretty substantial in these cases.
 10 So there was still some time less than 90
 11 percent saturation, but it was substantially
 12 reduced by the combination of morphine plus
 13 ketamine. So is this a true opioid-sparing effect,
 14 then? You use less opioids and you had decrease in
 15 the respiratory depression, at least measured by
 16 the saturation in the post-op period.
 17 Finally, a pretty new study, Myhre in
 18 Anesthesiology in volunteers, randomized,
 19 double-blinded, crossover study, used a
 20 remifentanil infusion, and used it not just as a
 21 continuous infusion, but did it to a target effect
 22 concentration, a TCI, of 0.6, 0.12, 0.24 nanograms

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1 per milliliter, and then the remi plus pregabalin,
 2 150 milligrams PO.
 3 They did an analgesic study in the
 4 laboratory. So they did a cold pressor test, a lot
 5 of different kinds of pain, although that cold
 6 pressor test is the kind of pain stimulus you want
 7 to use for opioids. But if you look at the
 8 left-hand panel, he's got placebo, the top curve,
 9 plus pregabalin plus placebo, the second curve,
 10 which pregabalin did a little bit. Remember, that
 11 was just one dose, so that was pregabalin alone. so
 12 there was no remifentanil. So it decreased the
 13 pain score by visual analog scale a little bit by
 14 itself. And that should be the horizontal line
 15 across because there was no remifentanil being
 16 given.
 17 Next curve down is the no pregabalin plus
 18 remifentanil, and you can see the decrease in the
 19 pain score as the target effect concentration of
 20 remifentanil goes up with a pain score of 70 to 80
 21 at the placebo beginning control, and then down to
 22 less than 20 with 2.4. And the pregabalin shifted

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1 that curve.

2 If you look at it, you can see that the pain

3 with pregabalin at 0.6, without pregabalin, you

4 need 1.2 to get the same pain score. And for a

5 pain score of 30, with pregabalin, you only needed

6 1.2 nanograms per milliliter. But without

7 pregabalin, you needed 2.4 nanograms per

8 milliliter. So really half the amount of effect

9 site concentration that was needed with

10 remifentanil with 150 milligrams of the pregabalin.

11 Over the right-hand side, you can see what

12 they looked at as far as the respiratory effects.

13 The problem of looking at just resting ventilation

14 is the effect is divided up into two variables.

15 They're divided up in the increase in CO2 and the

16 decrease in ventilation, so it's a little hard to

17 tease out. You may not see a significant effect

18 because the effect is distributed over 2 variables.

19 Pregabalin alone had very little effect on

20 ventilation end-tidal CO2. As you added increase

21 effects of the remifentanil, we know it's potent

22 respiratory depression, and you can see that the

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1 end-tidal CO2 for the high dose of remifentanil got

2 up to almost 50 millimeters of mercury, and we know

3 how big a stimulant that is. And there was more or

4 less an additive effect of the pregabalin. In

5 other words, there was a further increase in the

6 end-tidal CO2, a further decrease in the

7 ventilation.

8 So opioid sparing, yeah, because you have a

9 lower dose, and opioid sparing on the respiratory

10 effects because there's a pretty much straight

11 line, linear dose response curve. If you used less

12 opioid at 1.2 versus 2.4 TCI nanograms per

13 milliliter, it has less respiratory effects. So it

14 spared both the analgesia and spared the

15 respiratory effects of it; one of the few studies

16 in which you've got good respiratory measurements,

17 and perhaps not great, but at least trying to make

18 some solid analgesic measurements.

19 The recommendations that I can throw out

20 there is that early studies done in volunteers in

21 the laboratory really should include some of the

22 better, more precise measurements, of respiratory

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1 function, the hypercapnic ventilatory response and

2 maybe the hypoxic ventilatory response, with some

3 assessment of analgesia, just doing the respiratory

4 sparing effects by themselves, and should have a

5 dose-response effect.

6 So you can do, as I showed in this last

7 study, some comparison of where the dose is with

8 the adjuvant and without the adjuvant in the same

9 group of volunteers.

10 Acute pain, late clinical efficacy, you've

11 got to at least be measuring continuous saturation

12 and continuous pulse oximetry saturation and

13 continuous end-tidal CO2 in the acute post-op

14 period, and may need some special overnight

15 monitoring in patients like sleep apneic patients

16 who are at high risk for desaturations because of

17 obstruction, which is affected by the opioids but

18 wouldn't be picked up when you are trying to

19 measure something, and they're awake, and they're

20 breathing on the apparatus, and you're measuring

21 the ventilation; or they're in the recovery room

22 and the nurse is talking to them. But they get up

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1 on the floor, and now they fall asleep, and they

2 don't have their CPAP machine on, and they're going

3 to desaturate.

4 Chronic pain, I don't know. There's really

5 no accepted methodology that I know of to measure

6 respiratory effects in the chronic opioid user. I

7 think if you've got a patient with things like

8 sleep apnea, you can do home-based overnight sleep

9 saturation studies pretty readily now. Measuring

10 sleep saturations at home on a chronic pain patient

11 I think would be the minimum that should be done,

12 and maybe perhaps formal sleep studies also should

13 be done with that.

14 So finally, I think Richards back in 1953

15 had a good description. "Breathing is a truly

16 strange phenomenon of life, caught between the

17 conscious and the unconscious, and peculiarly

18 sensitive to both." Thank you.

19 (Applause.)

20 DR. RATHMELL: We'll take questions right at

21 the end. We're just about there.

22 DR. WARD: Perfect.

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1 DR. RATHMELL: Thank you, Denham.
 2 All right, John Markman, last but not least,
 3 and then we'll have a panel for plenty of question
 4 and answer time. John is professor of neurosurgery
 5 and neurology and director of the translational
 6 pain research program in the Department of
 7 Neurosurgery at the University of Rochester. And
 8 he's going to talk to us today about the patient
 9 improvements and group differences that would be
 10 clinically meaningful; so kind of get at that all
 11 elusive clinical meaningfulness.
 12 Presentation - John Markman
 13 DR. MARKMAN: First, I want to thank Bob and
 14 Dennis, Valorie and Shannon and Jen, and all the
 15 folks at IMPACT and ACTTION. It's a particular
 16 honor to speak with this group, obviously, the most
 17 important minds probably in our field. So it's
 18 really an honor. It's a little daunting because
 19 Bob would send out the agenda about every 3 days.
 20 (Laughter.)
 21 DR. MARKMAN: This is sort of like the
 22 Rolling Stones opening up for The Partridge Family.

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1 (Laughter.)
 2 DR. MARKMAN: I see this every day.
 3 (Laughter.)
 4 DR. MARKMAN: And now, just to make it a
 5 little worse, I got half the people here just
 6 killing my talk, giving brilliant talks on my
 7 topic. Shannon, with a brilliant encyclopedic
 8 analysis of literature; Brett covering, in a very
 9 cogent way, some analysis about the chronic pain
 10 trials; Nat of course fast forwarding us to July
 11 27th and giving us the concluding paragraph of the
 12 paper in the first talk.
 13 MALE VOICE: It's already written.
 14 DR. MARKMAN: So there's a lot of pressure
 15 here, but I'm going to try. The good news is it's
 16 probably going to be a little shorter than it
 17 otherwise would have been, so that's the silver
 18 lining.
 19 I'm going to talk about clinical
 20 meaningfulness. I think, as Raj said, when you get
 21 this invitation, you begin to really begin to
 22 marinate these questions. You'll see some of my

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1 patients here. These are some of my influences and
 2 our relationships.
 3 Here's the premise for my presentation.
 4 It's really this. Obviously, as you've heard
 5 today, over and over again, there's an enormous
 6 amount of uncertainty about just who should be on
 7 long-term opioid therapy, so who should take off on
 8 this plane. But I think we've also come to
 9 appreciate that there's probably more uncertainty
 10 about how to land that plane once you've taken off,
 11 and where to land. And there are a lot of
 12 different ways or whether to land at all. So I
 13 think that not only are there questions about who
 14 to take off and when to take off, but there are
 15 even more questions about how to land. So there's
 16 a lot of uncertainty about opioid sparing.
 17 So because so much of my talk was covered
 18 better than I could cover it, I'm going to show
 19 some home movies from my clinic. These are two
 20 patients I've seen over the last 6 days who made me
 21 think about this presentation. The woman on your
 22 left is kind of a refugee. She spent her life

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1 living in the Catskills, far east of where I live
 2 in western New York. She was getting older, and
 3 she had a very debilitating spinal syndrome. She
 4 basically has had this slow burning cauda equina
 5 syndrome
 6 She had her hardware removed in around 2011,
 7 and her scoliotic deformity began to progress, and
 8 she's basically ringing out her cauda equina, her
 9 nerve roots, like a wet dish rag over the last 7 or
 10 8 years. She was managed, I think quite expertly,
 11 in her native region in the Catskills, but as she
 12 lost function in her legs progressively, they
 13 looked like little stork legs, and over her bowel
 14 and her and her ability to stand, she basically
 15 capitulated and decided to move to Rochester, where
 16 her son who's sitting behind her lives.
 17 So she was something of an opioid refugee,
 18 and this is not uncommon. It's interesting that I
 19 was actually one of the advanced visit she made to
 20 Rochester before she moved in with her son because
 21 she didn't want to move until she knew that she had
 22 her therapy buttoned up. She was on buprenorphine

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1 for her pain after being on other opioids for a
2 long time and had very good relief. But she didn't
3 feel comfortable making this move until she knew
4 that she had a plan in place. So I met with her
5 and her son several times before she actually made
6 the move. And we're going to hear from her and
7 what she thinks about clinical meaningfulness.
8 This other gentleman is a very successful
9 entrepreneur in our city, owns a lot of real estate
10 and other businesses, but he had an aortic
11 dissection, and when he clotted off his aorta and
12 his iliac arteries, you can see that he lost his
13 right leg, lost a lot of tissue in his left leg,
14 and he has chronic neuropathic pain from his
15 dissection and the surgeries that ensued.
16 I think my take-home for listening to these
17 videos and helping you think about these patients
18 and how I approached this problem, it's really
19 embedded in the context of patient stories.
20 When you read clinical trials and you look at the
21 data, in some ways, it's confusing and it's hard to
22 interpret because it requires a lot of statistical

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1 knowledge, and it requires you to pay attention and
2 understand the methods very deeply, as you've heard
3 today.
4 But what it does in a way I think, which you
5 don't get unless you hear these patient's stories,
6 is it takes it out of context. So I want to take
7 some of the important issues, which you've heard
8 really clearly discussed, and hopefully put them in
9 the context of the voices of these patients.
10 Now, let's hope the video works.
11 (Video played and transcribed.)
12 WOMAN: I obviously would love to have a
13 straight spine, and be out of a wheelchair, and go
14 back to doing things that I did when I wasn't. I
15 have a fairly high pain threshold, I think.
16 MAN: I do, too.
17 WOMAN: When I say I need medication, I
18 don't do that easily. It's not a stigma, but I
19 just don't like medication, but I recognize I need
20 it for some things that I'd be stupid not to take
21 it. So I don't think anybody is arbitrarily saying
22 to me, "Your dose is too high; reduce it," without

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1 being aware of my situation, as Steve said. It's
2 the wrong question, and it's the wrong action.
3 DR. MARKMAN: So we had a discussion. I
4 mentioned to her that I was coming to this meeting,
5 and we were thinking about opioid sparing and
6 whether she would consider lowering her dose, and
7 how would we do it. And that's the video that sort
8 of set up this discussion.
9 She had just had a flare of her pain, which
10 she has these episodic flares. They last about 24
11 hours. She has them very infrequently. She has
12 extraordinarily good pain control on buprenorphine.
13 But she did have a flare, so she was particularly
14 apprehensive about the thought of lowering her
15 opioids. And some of the papers, which I'm gonna
16 talk about, especially one by Mark Sullivan, I
17 thought there were some really beautiful paragraphs
18 talking about the apprehension and how that related
19 to the clinical trial.
20 I think it's important also to understand
21 why buprenorphine was used in this patient. I
22 think it's particularly apropos given the talk we

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1 just heard by Dr. Ward, which is brilliant.
2 Obviously, buprenorphine has these unique features,
3 and I think one question I have in my own mind,
4 buprenorphine has this attenuated effect on
5 respiratory depression relative to other opioids,
6 certainly relative fentanyl, and I'll show you a
7 little slide about that. But the bottom line is
8 whether that's an opioid-sparing strategy drug,
9 which is a partial agonist and antagonist to a
10 receptor of the opioid pathway. Is that an
11 opioid-sparing therapy?
12 Dr. Fields and I were talking about that
13 this morning over breakfast. As Dennis said, the
14 beauty of this meeting is a lot of the intellectual
15 ferment occurs in the breaks and over dinner, and
16 I've changed my talk 4 times after breakfast.
17 This is a picture of her spine.
18 Unfortunately, this was almost 11 years ago. Her
19 spine is completely folded in on itself at this
20 point. But just to give you a drama, that picture
21 doesn't tell the whole story but just gives you a
22 sense of the situation. And for those of you who

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1 don't practice every day, this is what you look at
2 all day long. We don't look them in the eye
3 anymore; we look at screens like this.
4 This is a screenshot from Epic, which is the
5 electronic medical record. And this is the order
6 form to order her buprenorphine. And you can see
7 if you look closely here, inside this, there is a
8 box there, which is in yellow, which has, "single
9 dose at 24 milligram exceeds the recommended
10 maximum, 16 milligrams" -- this is the dose she
11 came to me on, actually -- "by over 50 percent,"
12 and I've got a couple of choices.
13 The first choice for override reason, is the
14 benefit outweighs the risk. I usually choose this.
15 (Laughter.)
16 DR. MARKMAN: It seems like a good defense,
17 right? But you've got about 6 others. When you're
18 using the system all day long, you get a little
19 paranoid. You think that immediately, Cellino and
20 Barnes gets an immediate copy of anything you put
21 in this box. They get a carbon copy. That's the
22 personal injury firm in our region. And another

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1 one goes to the DEA, and then you press on this
2 box, and you send the script off to the pharmacy
3 because you just have this sense that it's all
4 being monitored by some other third party that you
5 don't fully understand.
6 But you get these warning messages all day
7 long as you're writing opioids and taking care of
8 patients because you want to live in a world
9 where -- we're more and more in a world where
10 50 milligrams is magical, or 120, or 180, and it's
11 a one-size-fits-all world. But this woman doesn't
12 have a one-size-fits-all spine. You don't walk
13 into the running store in America and only have a
14 size 8 shoe or a medium sweater at the department
15 store. It's just not the way it works. Right?
16 I mean, personalization is probably one of
17 the calling cards of our system. And yet here,
18 when you try and personalize her care for her
19 particular situation, whether this is the right
20 decision or wrong, or whether you think the benefit
21 outweighs the risks, you're immediately getting
22 these warning morning messages. And if I'm worried

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1 about it, and this is what I do, and I've been
2 doing it for 20 years, then you can imagine
3 someone -- this is why she's a refugee. This is
4 why she's wandering around looking for someone to
5 write her medication.
6 So I just threw this in just now because I
7 was listening to Dr. Ward, and I've always loved
8 this slide which basically looks at the risk of
9 respiratory depression and the margin of safety of
10 buprenorphine relative to fentanyl. And what you
11 see here is the differential effect of
12 buprenorphine on respiratory suppression relative
13 to fentanyl. And you can see that fentanyl
14 continues to drive down that liters per minute,
15 where it doesn't really happen with buprenorphine.
16 It kind of plateaus there.
17 Again, is this an opioid-sparing strategy?
18 I don't know. We've heard from Dr. Katz earlier
19 that there are all these endocrine effects of
20 opioids, maybe the most important set of side
21 effects. Some people would argue that
22 buprenorphine does not agonize and affect the

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1 pituitary axis in the same way that other opioids
2 do. On the other hand, I don't really know. I do
3 check that routinely, but in her case, I don't know
4 if I'm making her osteoporosis worse and making her
5 curve worse by keeping her on opioids sometimes,
6 but it certainly occurs to me.
7 So I think I want to begin with this simple
8 point about relevance and clinical meaningfulness.
9 Opioid sparing may only be clinically relevant if,
10 as Dr. Hertz said, the risks of long-term opioid
11 therapy outweigh the benefits. When you begin to
12 think hard about opioid sparing is when the risks
13 of it outweigh the benefits. Now, it's not always
14 so easy to see. Obviously, I wouldn't click that
15 button if I didn't think the benefits outweighed
16 the risks. I wouldn't take that risk. It's also I
17 think, as my breakfast conversation with Dr. Stacey
18 made me apparently and abundantly clear, not really
19 appropriate until non-opioid treatment options are
20 exhausted.
21 So those are the two premises or the two
22 first checks. You have to ask yourself. And then

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1 I guess -- as we've talked about a lot today, and
 2 it's an insight I've kind of had over the last
 3 couple of weeks, but it seems like I wasn't the
 4 only one -- that opioid sparing may not make sense
 5 if there's a loss of analgesia. And again, there
 6 are other reasons, which we've already talked about
 7 extensively about why opioid sparing may not make a
 8 lot of sense.

9 I'm not going to dwell on these core
 10 domains, which I thought a little bit about from
 11 the studies I looked at. Obviously, in all of
 12 these studies that look at opioid sparing, there's
 13 a focus on pain intensity and all the things that
 14 IMMPACT has focused on over the last 15 years and
 15 over 90 publications. There's obviously a lot of
 16 consideration of mood, and quality of life, and
 17 physical functioning. You heard
 18 Dr. Haythornthwaite talk about the negative affect
 19 of opioids.

20 But I think the focus of the opioid-sparing
 21 outcome domains that I think are really the core of
 22 this meeting that we have to really hash out are

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1 those related to dose reduction. Is there a magic
 2 number? Which it seems like there's not a lot of
 3 consensus that there is, but certainly that's been
 4 the primary endpoint of almost every study that's
 5 been done in this field. The primary is always the
 6 amount of opioid reduced that I've seen, or very
 7 commonly. Shannon showed you others that weren't,
 8 but many of them were.

9 Obviously, this other question about opioid
 10 side effects and which are the serious ones and
 11 which are the nuisances, as we heard earlier. So
 12 some of these are nuisances and some of them are
 13 fatal, and how do we rank those and how do we
 14 prioritize those? That's that top circle.

15 So I'm not going to fill in these circles.
 16 I had a little bit more on this, but I thought
 17 Dr. Raja did a fantastic job talking about, for
 18 example, in the upper-right circle, what the opioid
 19 side effect measures would be, and how they would
 20 compare, and what we understand about them, and all
 21 their measurement characteristics, so I'm going to
 22 skip that.

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1 I'm going to focus on this study, which I
 2 really liked because it taught me a lot. When
 3 you're doing a talk, you always have to pick the
 4 study that you're going to pull yourself into the
 5 topic with. I love Mark Sullivan's writing, so I
 6 decided to focus on this one after Shannon and I
 7 talked about it or corresponded about it.

8 This is a prescription opioid taper support
 9 for outpatients with chronic pain. What they set
 10 out to do is demonstrate the feasibility of a
 11 prescription opioid taper support intervention.
 12 This was patients who had listened to a 14-minute
 13 video about someone who'd come off opioids and felt
 14 better, and then when they would have this series
 15 of interactions with a physician's assistant, who
 16 is specifically trained by some of the principle
 17 investigators in this study. And they'd go through
 18 a series of visits. It really gave them
 19 state-of-the-art cognitive behavioral care and
 20 other interventions.

21 The study looked at 22 weeks of the active
 22 treatment -- at the 22-week landmark analysis.

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1 They looked at mean reduction in opioid dose, and
 2 it was 43 milligrams lower in this opioid taper
 3 group than it was in the folks who were in the
 4 as-usual care. Now, this wasn't statistically
 5 significant. The author said, "The difference
 6 observed between groups in our study are clinically
 7 meaningful." As Shannon pointed out, no reference.
 8 Bit Mark Sullivan is like a philosopher king. Do
 9 you know what I'm saying? He doesn't need a
 10 reference.

11 (Laughter.)

12 DR. MARKMAN: I mean, he just laid it out,
 13 right? I was like, "Okay." I mean, it's good
 14 enough for Mark; 43 sounds good. It's manifest. I
 15 think we're done. And it's curiously close to
 16 number 42. For those of you who ever read the
 17 Hitchhiker's Guide to the Universe, where the
 18 answer for the whole meaning of the universe is 42,
 19 I thought that was curious. I mean, I wondered if
 20 he rounded up or something like that.

21 (Laughter.)

22 DR. MARKMAN: So was this study instructive?

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1 What did I learn from reading this study? Patients
 2 randomized to taper support intervention had a
 3 lower pain interference score. They had higher
 4 self efficacy for managing pain at both 22 and 34
 5 weeks. They did well, and they harnessed all these
 6 nonpharmacologic tools, and they reduced their
 7 opioid related psychosocial problems. They had
 8 more interest in their usual activities, these
 9 so-called emotional hijacking that goes on with
 10 high-dose opioids. They had less trouble
 11 concentrating. They felt less down and sluggish.
 12 It's something, when you put patients on
 13 buprenorphine, it's obvious immediately that that
 14 aspect of some of those opioid toxicities kind of
 15 goes away. Again, we were talking about that this
 16 morning. It's one of the most vivid things as a
 17 clinician that you see when you put a patient on
 18 buprenorphine.
 19 It showed the benefits, with the opioid dose
 20 reduced, that patients did not have a significant
 21 increase in pain severity. So there wasn't that
 22 trade-off that we talked about where they had lower

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1 opioids but they were somehow writhing in pain.
 2 No, they had lower opioids and they had less pain.
 3 So all good. Who could argue with this? And there
 4 was no difference in the levels of opioid misuse,
 5 depressive symptoms, or opioid controls concerns.
 6 But this is the part that really didn't sit
 7 well with me. This was called a feasibility study.
 8 The whole point of this study was to show
 9 feasibility. And I'm not a great math person. The
 10 primary barrier to feasibility in this intervention
 11 was recruiting and enrolling patients. It took
 12 3 years to recruit 35 patients who were randomized,
 13 so basically a little under 1 patient a month. I'm
 14 not great at math, but that's a problem. A lot of
 15 us see 35 patients a day, so that's an issue.
 16 What went on there, and why did it work out
 17 that way? They only enrolled 35 of the 144
 18 patients who were referred to them. Only 72
 19 percent of the patients went to most of the
 20 sessions, but basically they're enrolling about
 21 fewer than 1 patient a month, somewhere right
 22 around 1 a month.

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1 So excluded patients with current
 2 substance-use disorders, but allowed past
 3 substance-use disorders. I always think I never
 4 understand this idea. It seems to me that those
 5 are the patients who we're most concerned about
 6 here. That's the most clinically relevant
 7 population. In some sense, those seem to me like
 8 the patients who are more likely to die. They're
 9 more likely to have opioid problems. They're more
 10 likely to have -- what Dr. Strain talked about.
 11 They're more likely to give their opioids to
 12 someone else in exchange for something else and
 13 cause that societal burden. Why are we excluding
 14 them?
 15 The study didn't use buprenorphine. For me,
 16 buprenorphine has been a godsend in my practice. I
 17 could never successfully taper patients off very
 18 high doses to low doses. It took too long and was
 19 too hard. You'll hear another study, which a
 20 debunks or counters that notion. But it was a very
 21 hard, laborious thing to get patients off opioids.
 22 With buprenorphine, you can land the plane in no

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1 time. It's like a Harrier jet. You can just get
 2 them right down.
 3 Now, whether that's really just opioid
 4 rotation and not opioid sparing, I think that's a
 5 debate which is legitimate we could certainly have.
 6 But this study had more important limitations. It
 7 was unblinded, it was underpowered, and it was done
 8 by a single provider. So I don't know if this is
 9 feasibility in my book.
 10 So let's talk about the clinical importance
 11 embedded in clinical context. This is this notion
 12 I want to put to you that you really can't really
 13 talk about meaning and significance, at least with
 14 inpatient, until you really hear the story.
 15 (Video played and transcribed.)
 16 MAN: Yeah, I fought hard not to increase my
 17 dose when was on there, but I did it because I
 18 didn't want to become more dependent on it and put
 19 more in my system. So I stayed, but I could see
 20 very easily to just get a relief to take more.
 21 It's addicting. It is addicting, and you kind of
 22 lose that edge because you build up a tolerance in

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1 your system.
 2 DOC: Is your pain severe without pain
 3 medication.
 4 MAN: Oh yeah.
 5 DOC: And where do you have it?
 6 MAN: Generally from my hip down.
 7 DOC: And what does it feel like from the
 8 hip down?
 9 MAN: Burning, pins and needles. You can't
 10 function.
 11 DOC: You have in your phantom as well as in
 12 your --
 13 MAN: On your phantoms once in a while. I
 14 get a big tingle, like a big twitch once in a while
 15 in my -- where my right leg used to be.
 16 DR. MARKMAN: One thing I want to just take
 17 away from that, I think patients are always -- many
 18 patients but not all. And again, I think that one
 19 of the things that Eric's lectures have taught me
 20 over the years is that the cardinal feature of
 21 opioid-use disorder is loss of control. This is a
 22 story which I often hear, which is kind of the

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1 opposite to me. This is someone who's doing their
 2 own opioid sparing thing in his head all the time.
 3 He said I'm trying not to increase my dose.
 4 I hear that all day long, and especially
 5 now. But even 5 years ago, patients are constantly
 6 trying to do their own opioid sparing thing to
 7 minimize how much they're taking. And he tells you
 8 it's addictive. He tells you he gets euphoria, and
 9 he feels --
 10 (Video played and transcribed.)
 11 DOC: So is being on a lower dose important
 12 or is it more important not to have those ups and
 13 downs?
 14 MAN: It's better not to have the ups and
 15 downs.
 16 DOC: So the absolutely doesn't matter. If
 17 you were on 180 milligrams of OxyContin but didn't
 18 have those ups and downs, or 16 milligrams, or
 19 10 milligrams of buprenorphine and didn't have
 20 those ups and downs, that would be better than
 21 being on half the amount of oxycodone or half the
 22 amount of buprenorphine. Is that what you're

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1 saying?
 2 MAN: I don't know. When you -- I also
 3 think that some people, with the OxyContin, they
 4 keep on wanting more because that kind of gives
 5 them a euphoric kind of like -- I don't know, kind
 6 of gives you like a -- I don't know -- like a -- I
 7 will say a stone feeling.
 8 DR. MARKMAN: So this issue, he's noticing
 9 the focus on dose escalation over time and
 10 tolerance. But he's also telling you the one thing
 11 we really haven't talked about much today is this
 12 idea of micro withdrawal and the hyperalgesia
 13 withdrawal. We heard a little bit about it before.
 14 But to what extent is that something important to
 15 look at? Rather than absolute dose, what about
 16 just those fluctuations?
 17 So the happiness of most people we know is
 18 not ruined by great catastrophes or fatal errors,
 19 but by the repetition of slowly destructive little
 20 things. And obviously, this epidemic and the
 21 opioid crisis is marked not only by catastrophes
 22 and fatal errors, of course it is, but there are a

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1 lot of patients out there who, again, are tortured
 2 every day with these slowly destructive little
 3 things like intermittent withdrawal. And I think
 4 that's important to think about also and why that
 5 might be a clinically relevant endpoint.
 6 You saw this study -- or this is a big
 7 review that was done in the Annals of Internal
 8 Medicine. Brett did a really nice job abstracting
 9 from this, and so did Shannon. Again, they had a
 10 filter. They asked two main questions. They asked
 11 about the effectiveness of strategies to reduce
 12 long-term opioid therapy.
 13 They basically focus on all the things you'd
 14 expect them to focus on, so I won't even go into
 15 it. But they looked at 3,522 abstracts. They got
 16 it down to 67, and these people were very finicky.
 17 They only liked 3 of these studies. I mean, they
 18 really basically hated everything. I would never
 19 want to go out to eat with these people.
 20 (Laughter.)
 21 DR. MARKMAN: They liked 3 studies, the tiny
 22 ones. And they looked at all different kinds of

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1 stuff, interdisciplinary pain programs;
2 buprenorphine assisted dose reduction; behavioral
3 interventions; detoxification; ketamine;
4 acupuncture; some other cognitive behavioral
5 approaches; lidocaine infusions. They did the
6 whole waterfront.
7 They came across -- what you've heard
8 already, that some of this literature -- I like the
9 word that Nat used, that opioid-sparing studies
10 tend to be dosed centric. It's like one of these
11 hallmarks of an opioid-sparing study is like how
12 much did you take? So they looked at that in many
13 of these studies.
14 One of the studies they liked quite a bit
15 showed this reduction of 10.1 in the active
16 treatment arm with CBT and mindfulness meditation
17 as compared with usual care. But none, as you'll
18 note here, were powered to detect clinically
19 meaningful differences in opioid-dose reduction.
20 They don't tell you how you know exactly what those
21 clinically meaningful doses are, but they just tell
22 you that none were powered for that. So again,

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1 it's uncertain.
2 This is the Cochrane review, which just
3 underscores, as Brett told you, the fact that we
4 don't really have a literature to rely on. This is
5 why we're all together in this bunker.
6 (Laughter.)
7 DR. MARKMAN: We're here to sort this out,
8 and we won't leave until we do it. So we're going
9 to figure out what that number is. There are
10 different ways to think about this. One way to
11 think about it, as is kind of responder analysis
12 where you will have this menu of different where
13 you put together these different features into a
14 little bit of a composite, I think. Obviously,
15 Dr. Simon knows a lot about that and has done that
16 in fibromyalgia. But I was thinking that a
17 composite of some type might be one way to solve
18 this, no worse pain, a little bit stable function,
19 but a reduced dose. And that would be the sausage
20 that we try and make here.
21 I just want to talk about this study. I
22 learned about it this morning after breakfast from

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1 Dr. Fields, and I thought this was quite
2 interesting. This is just a research note from
3 JAMA Internal Medicine, and this is from the
4 Stanford group. This is a totally different model
5 than the one I gave you earlier. This is about not
6 using a physician's assistant, but this is about a
7 community-based clinic, a single clinic, partnering
8 with a physician.
9 So there's a contract, which is renewed
10 between the patient and the physician in this
11 model. And they agreed to reduce the dose over
12 4 months. There are 2 steps a month; 110 patients
13 were screened. And in contrast to the one you
14 heard from the University of Washington, here you
15 had 82 of 110 actually enrolling, so there was
16 something very compelling about the way they made
17 their offering. And again, it was this 5 percent
18 reduction and then increased to 10 percent
19 reduction per week between months 2 and 4.
20 They relied on -- I thought this was a very
21 good feature. They looked at the prescription drug
22 monitoring database in their state. They looked at

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1 your in-tox screens. So they were trying to a
2 little bit get at that societal piece that Eric was
3 talking about and all the potential adverse events
4 that could occur with an opioid-sparing program at
5 the societal level.
6 The primary endpoint of course here was the
7 change in MEDD from baseline, and pain intensity
8 was a secondary endpoint. So there are a couple
9 limitations here. One is that 31 out of 82
10 patients dropped out, so there's clearly something
11 about this method, which probably needs to be
12 refined before it gets scaled. But the median
13 baseline dose was quite high. I was struck by
14 this; 288 milligrams, and the average patient had
15 been on medication for 6 years.
16 The median dose was reduced to 150
17 milligrams. The likelihood of a greater than 50
18 percent dose reduction was not predicted by the
19 starting dose, by the baseline pain intensity, by
20 the years prescribed opioids, or any other
21 psychosocial variable. So I was struck by that.
22 This is their conclusion, which I thought,

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1 again, flew in the face of what I told you earlier
 2 when I said I used to have a really hard time
 3 getting patients down off their high-dose opioids
 4 before buprenorphine. They said, "Our data
 5 challenged the common notions," held by myself and
 6 others, "that patients taking high-dose opioids, or
 7 that the duration of opioid dose predicts taper
 8 success."
 9 So I thought this was a really interesting
 10 paper. It's just a research note. It's a very
 11 small addition, but I'm grateful to Dr. Fields for
 12 pointing it out to me.
 13 For the dose-centric, which I think some of
 14 us are, or at least feel like this will be part of
 15 the equation here, there are different ways to
 16 think about this. But one of the things I'm
 17 struggling with is do we think about a patient who
 18 takes 6 Percocets intermittently and very
 19 strategically, differently from the patient who is
 20 on a round-the-clock opioid at 90 milligrams every
 21 day?
 22 I think about them different clinically.

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1 Clinically, that means something very different to
 2 me. The patient who says I don't take it for
 3 5 days; I never get withdrawal. But if I decide I
 4 want to go play squash, or garden, or take my kids
 5 on the boat, then I take 3. And again, I look at
 6 those patients differently, and I wonder if we will
 7 as well as a group.
 8 Again, the question is how small is too
 9 small? "If you think you are too small to make a
 10 difference, try sleeping with a mosquito," a famous
 11 quote from the Dalai Lama.
 12 Then I think here is one of the biggest
 13 questions that I think we have to sort out. And
 14 again, this has been said before, but I want to
 15 come back to it; what to do with the patient who
 16 comes to you on high-dose opioids who you want to
 17 taper, but who clearly has opioid-use disorder,
 18 who's clearly out of control or has a set of
 19 behaviors, which are distinctly unmanageable? So
 20 listen to this patient.
 21 (Video played and transcribed.)
 22 MAN: Whatever you can do; there's 21st

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1 century. It's got to be something out there that
 2 can help me.
 3 DOC: Okay. And again --
 4 MAN: Somebody's got to help me. I mean, I
 5 tried so many -- nobody wants to help me, it seems
 6 like.
 7 DOC: Why don't they want to help you?
 8 MAN: Huh?
 9 DOC: Why don't they want to help you?
 10 MAN: I don't know. I think it's because of
 11 all the medication, everything that I was on
 12 before. They're just scared of it because of the
 13 New York state laws, and they just don't know how
 14 to help me. Let's put it that way. That's the way
 15 I feel, sir.
 16 DOC: And what part of your body hurts?
 17 MAN: Everything?
 18 DOC: Your whole body.
 19 MAN: My whole body. My whole body's in
 20 pain.
 21 DOC: And this has been going on, remind me
 22 for how long?

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1 MAN: Since 1989.
 2 DOC: And it started just out of the blue,
 3 all day, one day, right?
 4 MAN: It just started -- I was working in
 5 a -- I was working on a doc, unloading trucks, and
 6 one day I just couldn't walk.
 7 DOC: And all of a sudden.
 8 MAN: And then all of a sudden -- and then I
 9 asked. They said because -- you know, I thought it
 10 was because of my heritage, because I'm half
 11 Spanish, I'm half Latin, and I'm asked Sicilian> I
 12 said, "Could it be that?" First they said it could
 13 be Lou Gehrig's. I've been through so much.
 14 DOC: Do you have Lou Gehrig's?
 15 MAN: No. I told you the doctor found out
 16 what I had was Dr. --
 17 DR. MARKMAN: I won't name names --
 18 (Laughter.)
 19 DR. MARKMAN: -- but that guy figured it
 20 out.
 21 So I was incredibly relieved when I saw this
 22 patient, and I realized that he wasn't on opioids

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1 when I saw him, so I did not have to taper him off.
 2 But this is a couple times a week, some version of
 3 this song. And it's not always this dramatic, but
 4 it's a reality. And I think that for these
 5 patients who are on high-dose opioids, I think,
 6 again, this is part of the complexity of what we
 7 face.
 8 I think that we can't exclude these patients
 9 like I see a lot of these trials doing. We've got
 10 to include these patients or at least we have to
 11 have a carve out of a way to study them as well.
 12 Because, frankly, I think that there are very few
 13 patients in my community who are still on high-dose
 14 opioids. A large family practice near me with
 15 24,000 patients, there's only 106 patients on 180
 16 milligrams of morphine a day or greater. I mean,
 17 there's just no one out there.
 18 So there aren't that many of these super
 19 high-dose patients. Even in 2011 in the VA, only
 20 4.5 percent of patients are on those super high
 21 doses. So there aren't that many, in fact, in 2018
 22 I think. So the question is what are we going to

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1 focus on? And I think this is one area I think
 2 that could be relevant.
 3 The central question for me and for all of
 4 us, I think, is are patient improvements and group
 5 differences to be considered differently in
 6 patients with acute and chronic pain and features
 7 of opioid-use disorder, as compared to patients
 8 with acute and chronic pain in the absence of
 9 opioid-use disorder? And I think that's one thing
 10 that we have to sort out.
 11 A caveat is most of the studies I talked to
 12 today examine voluntary participation in a clinical
 13 program or research intervention. The findings may
 14 therefore not be generalizable to patients for whom
 15 LTOT is reduced or discontinued involuntarily. And
 16 again, most patients I think in my life, and
 17 probably in other clinicians here, what they're
 18 told is -- just like he said -- know, "New York
 19 state won't let my primary care doctor do it
 20 anymore," or "His university won't let him do it
 21 anymore." "His practice administrator won't let
 22 him do it anymore." "It's sort of like the hand of

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1 God comes in and takes my opioids away." Nobody
 2 really wants to own that they don't feel
 3 comfortable prescribing for these folks anymore.
 4 So I think we have to think about ways of
 5 recruiting and enrolling and designing
 6 interventions for a world where there's going to be
 7 participants who don't want to participate in that
 8 activity, for whatever reason. Some of it -- well,
 9 you all understand those issues.
 10 So the consensus on what constitutes
 11 meaningful dose reduction is needed. Every study
 12 says that. You've heard that over and over again
 13 today, including patients transitioning to
 14 buprenorphine. And again, there's insufficient
 15 evidence, I think, with regard to adverse event
 16 reporting, and that's really going to be critical
 17 because I do think there are as many -- and I
 18 thought this was one of the really wonderful parts
 19 about Dr. Strain's talk is talking
 20 about -- changing things too rapidly I think has
 21 been one of the most catastrophic consequences
 22 here, saying we're going to just do an about face

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1 on what we've been doing for a very long time;
 2 we're going to go the other way. I think that
 3 there's been enormous unintended consequences of
 4 that.
 5 So I think that if we institute strategies
 6 for opioid sparing, we really got to think about
 7 how we're going to get the signal from outside
 8 where you're doing that, because clearly,
 9 developing abuse-deterrent opioids and doing other
 10 things have had other consequences more broadly for
 11 society.
 12 A few take-home points for the IMPACT
 13 guidance. There's obviously a need for consensus
 14 reporting regarding the appropriate opioid dose, or
 15 the range of doses, or what to consider when
 16 defining that dose. Obviously, that reduction is
 17 going to be different for the patient improvements,
 18 where it's probably larger than the group
 19 differences, where it's probably smaller.
 20 There's a need to specify treatment in study
 21 populations for whom dose reduction is not
 22 appropriate, I think a reasonable goal of therapy.

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1 And there's a need for consensus guidance on,
 2 again, reporting these adverse events, whether it's
 3 in PDMPs, or state police departments, or whatever
 4 social institution we need to harness, or
 5 Bluelight, however we're going to surf the
 6 internet. But the reality is we need other tools
 7 to pick up on the signals that we're creating when
 8 we institute opioid sparing on a more broad say.
 9 I'm going to stop there, and thanks so much.
 10 (Applause.)
 11 DR. RATHMELL: Fantastic.
 12 DR. MARKMAN: Thank you.
 13 Group Discussion
 14 DR. RATHMELL: All right. If everybody
 15 would come up to the front here, all the
 16 afternoon -- nope, all the afternoon speakers. You
 17 can come, too, if you'd like.
 18 (Laughter.)
 19 DR. RATHMELL: Some fantastic presentations.
 20 I don't know whether to be more dejected or more
 21 encouraged. So let's start with some questions,
 22 please. And remember, introduce yourself and tell

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1 us where you're from first.
 2 Rob?
 3 DR. EDWARDS: It's Brigham and Women's.
 4 Thanks very much to the speakers. Those were
 5 fantastic presentations. I think I have to
 6 rhetorical questions for John Markman. I will try
 7 and make them brief, and as a rhetorical you won't
 8 be obligated to answer.
 9 So rhetorical question number 1. Given your
 10 suggestion that opioid-sparing studies and
 11 treatments make the most sense, or perhaps only
 12 makes sense, when risks outweigh benefits, which I
 13 think is a terrific framing, should this group be
 14 recommending, when it comes time to make
 15 recommendations, that opioid-sparing studies be
 16 performed primarily or exclusively in high-risk
 17 populations?
 18 We essentially know what those high-risk
 19 populations are. Those are folks with a past
 20 history of substance Abuse, psychiatric disorders,
 21 high levels of psychological distress, and negative
 22 affect. I suspect that will be an interesting

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1 discussion point.
 2 Rhetorical question number 1, given that
 3 there's no consensus at all on clinically
 4 meaningful dose reductions, should we take a page
 5 out of the past clinical trials playbook, borrow a
 6 move I think from IMPACT and ACTION's past
 7 initiatives, and recommend something like a John
 8 Farrar style analysis of opioid-dose reductions,
 9 where we define some functional or patient-reported
 10 global outcomes and tie amounts of dose reduction,
 11 either in absolute terms or in percentage terms, to
 12 those functional and patient-reported global
 13 outcomes, and then hopefully come to some sort of
 14 consensus around a number or a range of numbers
 15 whereby that could serve as a generally agreed on
 16 benchmark for what constitutes a clinically
 17 meaningful dose reduction? And it wouldn't be
 18 perfect, but it would probably be a lot better than
 19 what we've got now.
 20 Thanks. That was longer than I meant it to
 21 be.CO2
 22 DR. RATHMELL: So I don't think they're

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1 rhetorical. G ahead.
 2 (Laughter.)
 3 DR. MARKMAN: The first one, I think I'll
 4 leave to others. I think that Brett and I had a
 5 conversation about this earlier, about whether
 6 everyone is not a candidate for opioid sparing.
 7 And he was adamant, I think, that there's a lot of
 8 toxicities of opioids that we're not really picking
 9 up on and not paying attention to. And if we just
 10 think about this too narrowly, we're losing the
 11 opportunity to avail patients of many
 12 non-pharmacologic strategies to control their pain.
 13 I think his underlying point was that we're
 14 too medication focused and centric and too opioid
 15 centric. I think that was his argument, or at
 16 least his point, that he was making a breakfast. I
 17 don't know, Howard, if I got it right or -- I think
 18 that was his point.
 19 So I'll stop there. I'll let others -- why
 20 don't we break them into two? Is that okay with
 21 you?
 22 DR. RATHMELL: Yeah. So stop there, but go

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1 on with the outcomes and whether or not this -- you
 2 kind of glanced over the idea of a composite
 3 outcome; a number of the speakers have. And what I
 4 think Rob's asked is can we combine some
 5 predetermined endpoints for functional improvements
 6 and get away from the idea of just opioid-dose
 7 reduction alone?
 8 DR. MARKMAN: Yeah. I've always been
 9 attracted to the idea -- first, I think this is the
 10 question that's being asked about composites. I
 11 think that's how we practice clinically. I think
 12 that's what we're asked being asked to do when we
 13 say that the risks outweigh the benefits; we're
 14 saying that the analgesic benefit is a 30 percent
 15 reduction in pain intensity and there are no major
 16 dose-limiting toxicities, which are causing me not
 17 to prescribe. And I think that's what we're often
 18 being asked to do.
 19 So I think, composites, I know that a Nat
 20 and Lee and I worked on a composite years ago for
 21 OMERECT, based on the Cox-2 data that looked at
 22 reduction in pain intensity, no deterioration in

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1 function using the Roland Morris, I believe, and a
 2 certain threshold on the Patient Global Impression
 3 of Change, and sort of put those three components
 4 together as a way of trying to capture, in a more
 5 holistic way, an endpoint that didn't just look at
 6 pain intensity reduction, or didn't just look at
 7 function, or just didn't look at satisfaction.
 8 DR. RATHMELL: Rob, did we get at the crux
 9 of your question.
 10 DR. EDWARDS: You did great. Thank you.
 11 DR. RATHMELL: Okay.
 12 DR. MARKMAN: Can I just say one last thing,
 13 though?
 14 DR. RATHMELL: Sure. I don't think it will
 15 be the last thing.
 16 (Laughter.)
 17 DR. MARKMAN: I agree. When I was on the
 18 plane this morning, I was thinking about, I really
 19 decided I was going to do an about face. I really
 20 didn't want to have to specify a milligram amount
 21 and say, well, this number of milligrams is the
 22 magic number. And I was really trying to avoid

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1 doing that. But I think as Rob was asking and
 2 challenging us to do, I do think specifying, and
 3 stepping up, and giving as clear and as even as
 4 quantitative a number as we can is incredibly
 5 helpful.
 6 I think one could argue that there's been
 7 nothing more catalytic, in terms of having folks
 8 interested in drug development in this area,
 9 interested in developing therapies and for our own
 10 questions, than knowing that a 30 percent reduction
 11 in pain intensity is clinically meaningful. I
 12 think that's had an enormous clarifying and
 13 accelerating effect on so many different research
 14 efforts all the way across the entire space.
 15 So I do think the more clarity we give, even
 16 if it's not a particular milligram, but anything as
 17 close to that as we can get, will accelerate
 18 things.
 19 DR. RATHMELL: Please, in the back.
 20 DR. SIMON: Simon, Boston. I'd just like to
 21 inform this discussion a little bit about a caveat
 22 that we discovered in some of the work that we were

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1 doing about drug safety, which has a significant
 2 impact on our ability to ascertain and measure
 3 these side effects that may be associated and a
 4 change in the side effects as being an outcome.
 5 We did patient fora to determine whether or
 6 not they actually report side effects in clinical
 7 trials and in clinical practice. And we actually
 8 had the oncology people come to this meeting, who
 9 actually informed us about a randomized-controlled
 10 trial where they actually used a patient-reported
 11 outcome side effects measurement system versus a
 12 clinician-ascertained side effect measurement
 13 system. And 20 to 30 percent of the patients would
 14 not tell their clinician about side effects, either
 15 in the RCT or in the clinical practice. And the
 16 reason they didn't want to tell was because they
 17 were fearful of losing access to the therapy.
 18 In the contextual discussion that John just
 19 led, it is really critical. If we're going to
 20 think that sparing is measured by a safety series
 21 of issues as it relates to the experience that the
 22 patient has, what is the context of how they're

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1 fearful about losing their pain medication, or
 2 losing their euphoria, or whatever it is that they
 3 are gaining from being on this medication?
 4 We were shocked at the results, and we were
 5 shocked what patients were telling us in our
 6 patient fora. We actually had over 40 patients
 7 that were international, that consistently told us
 8 the same thing.
 9 So it raises some questions about what we're
 10 thinking about measuring in the context of opioid
 11 sparing, and it really raises not just questions in
 12 milligram amounts, but it also raises questions
 13 about contextually the side effects and if you
 14 decrease the side effects. If you can't measure
 15 them in any other way besides asking the patient,
 16 will we really have data that we can actually use?
 17 DR. RATHMELL: And it depends on who asks
 18 them, is a big part of it.
 19 Any comments? Srin?
 20 DR. RAJA: I think that's a very important
 21 point, and that relates to some of the scales that
 22 have been used to, such as the self-report MADS

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1 scale versus the MADDERS. In that, one of the
 2 issues is in the self-report scale, when there was
 3 some anonymity, there's some suggestion of some
 4 patient honesty in what they're reporting as long
 5 as they feel that there are no direct consequences
 6 of that. Bit other scales may not have the same
 7 implication.
 8 So I think if you want to get the actual
 9 numbers of potential opioid-use disorders, a
 10 certain degree of anonymity may be important, I
 11 think.
 12 DR. RATHMELL: Please?
 13 DR. STEINER: Hi. It's Deb Steiner again.
 14 I have three things I wanted to just ask and
 15 clarify. One is talking about composite endpoints.
 16 And John Farrar, you can definitely correct me.
 17 But my understanding is that a composite endpoint
 18 is when you have to hit each of the predefined
 19 criteria, and a multicomponent endpoint is when you
 20 can hit one of the criteria.
 21 The reason I'm asking is not to be
 22 difficult. It's because I think there's a really

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1 important difference in, first of all, the idea of
 2 pain intensity, side effects, whether it's to hit
 3 one or both; and then the other is if the
 4 discussion's about side effects, nausea, vomiting,
 5 then the distinction is would it be acceptable to
 6 potentially hit only one of those?
 7 So if I'm off base, please somebody correct
 8 me.
 9 DR. RATHMELL: Who wants to take on
 10 composite versus the multicomponent where you can
 11 pass or fail on any one of a number of different
 12 predetermined components?
 13 Nat, do you want to take that on? I think
 14 that would be reasonable.
 15 DR. KATZ: I actually haven't heard that
 16 specific terminology before, but certainly there
 17 are differences --
 18 DR. STEINER: You haven't been at Biogen.
 19 DR. KATZ: -- I have actually been there a
 20 few times. But certainly there are different ways
 21 of constructing composite space on how people
 22 perform on the different components. It could be

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1 an "and" or it could be an "or" which I think is
 2 what you were saying.
 3 DR. STEINER: So the terminology forget;
 4 just the distinction I think is what's important
 5 for the discussion tomorrow.
 6 Then another point I just want to make
 7 coming from clinical development is I am all for
 8 rigorous trials and everything; I mean, definitely.
 9 But trying to propose a trial of 6 months,
 10 12 months duration, like was proposed a little bit
 11 earlier today, I think that's going to get -- it
 12 would just be difficult for sponsors to do that or
 13 for developers to get support for that. So that's
 14 just a point to keep in mind, not that I don't
 15 support it, just the realities of that aspect of
 16 it.
 17 Then my last point was, a little bit earlier
 18 today, it was a point made about opioid taper. And
 19 I think, Nat, that was in your discussion of study
 20 designs. And I just wanted to mention I was
 21 actually shocked -- and not in a bad way -- at AAN
 22 this past April. There was so much discussion

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1 about how -- and by people who treat pain, by
 2 people who are knowledgeable, how they're managing
 3 their patients, and experts asking other experts.
 4 So I just think that's a really important aspect,
 5 especially coming from the sponsor's side because
 6 the sponsors need guidance on that. That's all.
 7 DR. RATHMELL: On opioid taper?
 8 Do you want to add something, John?
 9 DR. MARKMAN: Your last question, your point
 10 about limiting to shorter duration studies, you
 11 mentioned the AAN. When I look at the duration of
 12 studies in other fields, 6 months, 9 months,
 13 4 years, 5 years, recent Alzheimer's trials, these
 14 are multiyear studies.
 15 Why is it not feasible to do a 6-month study
 16 or a 9-month study in our field? Obviously, these
 17 companies are clearly willing to undertake these.
 18 And partly because I think there's so much societal
 19 pressure to have more long-term evidence for
 20 analgesics. I mean, that's I think at the root of
 21 a lot of the narratives.
 22 DR. STEINER: I think that there are two

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1 reasons. There are other reasons. One reason is I
 2 think that people who work in pain are aware of the
 3 number of negative trials, and failed trials, and
 4 just the concern that the longer you go, is it just
 5 a waste, and should you do an interim analysis, and
 6 you have to make a bigger trial to save your alpha,
 7 and that type of a discussion.
 8 So I think that's a biggie. And the other
 9 is just, realistically -- and I don't know if that
 10 would be true in this type of study design, but
 11 they're just high dropout rates. I just think from
 12 the sponsor side, those are concerns.
 13 DR. STACEY: Brett Stacey. I want to say
 14 one more thing about that, too, which is, we give
 15 people long-term opioids expecting them to
 16 potentially be on them for the rest of her life,
 17 yet we have studies that are 12 weeks in duration
 18 upon which we base that. In the endocrinopathy,
 19 the depression effects, those are later effects
 20 that are not going to show up in those studies, and
 21 the difficulty with tapering, and the micro
 22 withdrawal.

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1 All those things have been discussed -- a
 2 lot of those things that have been discussed are
 3 long-term effects. And the reality is that it's
 4 difficult to have long-term studies. It doesn't
 5 mean that they're not needed and we shouldn't
 6 support them.
 7 DR. RATHMELL: Please?
 8 MS. COWAN: I think the thing you have to
 9 remember is you're tapering them off. They still
 10 have pain, so you're going to have to do something
 11 else for them. And I think that's a missing piece,
 12 that we're trying to taper them off opioids but
 13 what else are we doing to help them manage that
 14 pain? I mean, there are a lot of things, and I've
 15 said this before. But keep in mind as you taper
 16 them off, it doesn't mean their pain's going away.
 17 So what is -- I don't know.
 18 DR. RATHMELL: I think a number of us should
 19 respond to that. This is an everyday discussion
 20 that we have in the pain clinic that just says, but
 21 what about my pain? And the hard part is, after
 22 doing this for many, many years, you can taper in

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1 such a way that the report of the pain intensity
 2 doesn't change over time, you haven't abandoned the
 3 patients, and yet you really haven't added anything
 4 back into the mix that's really added meaningful
 5 new analgesia. That's a really difficult
 6 conversation, and it means a lot of trust over a
 7 long -- you can't do this the first time you meet
 8 somebody in the clinic.
 9 Do other people want to respond to that?
 10 Because I hear exactly what you're saying, and it's
 11 a conversation we have all the time.
 12 MS. COWAN: One of the things we always say
 13 is for people when they are told, "learn to live
 14 with it," that's not something any of us know how
 15 to do. It's not an instinct that we have. We have
 16 to teach them how to do that. And that's always
 17 been the missing link, is teaching them. And you
 18 can, but you've got to support them, which means
 19 providers, a whole group -- I mean, it takes that
 20 team. Someone had a team slide up there. But it
 21 does take a whole team, and that becomes expensive,
 22 so that's another whole issue.

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1 DR. RATHMELL: Anybody else on pane? The
 2 panelists are remarkably silent on this one,
 3 despite probably everybody having been in these
 4 shoes.
 5 DR. FARRAR: At the risk of interrupting,
 6 which I'm going to do anyway --
 7 (Laughter.)
 8 DR. FARRAR: -- it won't surprise folks.
 9 DR. RATHMELL: Who is that interrupting? I
 10 don't know.
 11 DR. FARRAR: John Farrar, a very quick
 12 comment. You asked about dementia trials and
 13 seizure trials. It's because seizures are easily
 14 to diagnose and dementia is something that is
 15 measurable over time with certain scales and other
 16 things that people have much more confidence in.
 17 You know and I know that I've got a patient
 18 who says every day, their pain is a 7 out of 10 and
 19 sometimes it's a 9 out of 10. You give them
 20 medication; it goes to a 7, and they come in,
 21 "Today my pain is a 10." We don't have scales that
 22 are appropriate for long-term studies because the

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1 zero to 10 scale is clearly not appropriate for a
 2 6-month or 12-month study. I had one patient I
 3 measured his pain in baskets. If he brought me a
 4 basket, it meant he was feeling better because he
 5 had the time to weave it. If he didn't bring me a
 6 basket, I knew he was in trouble.
 7 I don't know how to deal with that over the
 8 long term. I think one of the problems in the
 9 longer-term planning is how do you deal with that.
 10 The second is that as soon as people stop whatever
 11 medication that is being used, as Penny was just
 12 saying, other things get done, and the drug company
 13 is not interested in what happens to them after
 14 that.
 15 DR. RATHMELL: Let's move on to some other
 16 areas.
 17 Rick, do you want to --
 18 DR. RAUCK: Richard Rauck, Wake Forest.
 19 This is for Raj. Thanks, all you guys, for a great
 20 talk. In listening to everything today -- and
 21 since I have to do some of the moderating tomorrow
 22 for the acute pain stuff -- when I listened to all

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1 of those studies you showed on the epidemiology,
 2 and I think back to even Eric's comment, which I
 3 wrote down so I would get it right, which was just
 4 getting opioids to people is not the reason people
 5 misuse them.
 6 If I had to take away a message -- and I
 7 think it's relevant to why we think opioid sparing
 8 may be effective in acute versus chronic pain, and
 9 I'm more of a chronic pain guy than acute
 10 pain -- it sure looked to me like those
 11 epidemiology studies suggest and support that there
 12 isn't really increase abuse from just the exposure
 13 in the acute setting. Those were so small numbers,
 14 you could almost say that's less than what we would
 15 think of as the incidence of abuse just by general
 16 population parameters, 0.6 percent or 1 percent of
 17 Brett's work. I could even say that 4.1 percent
 18 versus 1.3 percent is 3 times higher, but maybe
 19 those people got opioids because they had a worse
 20 problem at the time of discharge. That
 21 relationship is not a cause and effect necessarily
 22 for why they're getting opioids.

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1 So I think it would be relevant if we all
 2 agree, or if you agree, or how we have that
 3 discussion, then we could move away from that we're
 4 going to do opioid-sparing trials in the acute pain
 5 for reasons other than just abuse, taking away a
 6 little bit I think Brett's point about more pills
 7 available. Let's leave that aside and the reason
 8 we might want to send them out with less pills.
 9 Do you think that's a fair conclusion, Raj,
 10 or would you draw something different out of all
 11 I've heard today?
 12 DR. RAJA: I think that's fair, but with
 13 some caveats. When I was looking at the first
 14 study which I presented on the Denver population in
 15 terms of patient hospitalization for acute pain in
 16 opioid-naive patients, I was impressed by the fact
 17 that a year later, the proportion of patients
 18 getting prescriptions in patients who were admitted
 19 for non-surgical indications were considerably
 20 higher, twofold higher than the patients going for
 21 surgery. You would think surgery would be clearly
 22 causing pain, but a number of those patients were

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1 admitted for non-surgical indications. Few of them
 2 were pain, chronic pain, but the majority of them
 3 are not chronic pain patients.
 4 So here is a population that were opioid
 5 naive to start with, had some kind of an acute
 6 episode that required hospitalization, and they
 7 were sent home with a prescription. And then 12
 8 months later, they seemed to have a higher
 9 proportion or higher risk for being maintained on
 10 opioids.
 11 So I think there's something inherent about
 12 being sent home with an opioid and continued with
 13 that, but what is that risk, and who are those
 14 populations at risk is important. This comes
 15 along, back to the questions that Bob initially
 16 posed, as should we have a composite measure or
 17 develop a meaningful dose reduction type of
 18 measure?
 19 I think that makes sense, but what we need
 20 is to define a clear dose-response relationship
 21 across different adverse effects. For example,
 22 respiratory depression clearly is dose related. At

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1 least in chronic pain patients, constipation
 2 doesn't seem to be dose related. Even with the
 3 first dose, they may appear to be constipated. And
 4 even in those large epidemiological studies, the
 5 risk of opioid-use disorder, there wasn't a clear
 6 dose-response relationship.
 7 So I think what we need to develop first is
 8 look at outcome measures, look at the different
 9 adverse effects, develop in which of these doses
 10 adverse effects are clearly dose related. And
 11 there, maybe you might shift the needle somewhat.
 12 But that requires more granular data on the
 13 different adverse effects and the relationship of
 14 those adverse effects to dose.
 15 DR. SANDBRINI: Friedhelm Sandbrink. I'm
 16 from the Washington D.C. VA medical center. I want
 17 to talk a little bit more, actually, about the
 18 effect of the dosage. By looking at our VA data,
 19 our patients on opioid medications in the past, who
 20 are taken off opioid medication; that's one data
 21 source that we have. And then, in particular, we
 22 have been starting to analyze all our patients who

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1 had a history of opiate exposure and then had an
 2 overdose or suicide in the recent years.
 3 What we find is that the majority of
 4 patients that die of an overdose of opioids are not
 5 on high dosage. Yes, individually speaking -- and
 6 I think that's what the graph showed of the
 7 Bonid [ph] study that we saw. Individually
 8 speaking, the risk is significantly elevated if you
 9 are at high dosage, but the majority of patients
 10 who actually die, 80 percent in the VA system are
 11 below 100 milligrams of morphine equivalent. The
 12 majority are 20 to 50 milligrams of morphine
 13 equivalent.
 14 When we look at the data of what drives the
 15 risk of an individual patient, the greatest risk
 16 comes from mental health comorbidities. That
 17 drives the risk. Any past admission to an
 18 inpatient mental health service or psychiatry
 19 service drives the rest 20 times; that's any past
 20 history, whereas in our study, the benzodiazepines
 21 drove it only by a factor of 1.4.
 22 So I think if you're talking about opioid

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1 sparing, we have to really study -- we're trying to
 2 shift from less risk to more benefit. And why are
 3 we making that equation? Which are the patients at
 4 risk?
 5 Now, the factor of co-prescribing sedative
 6 medication is another huge factor that we see in
 7 our data, and that includes what we consider
 8 evidence-based therapies for pain, such as the
 9 anticonvulsants that are sedating, muscle relaxant,
 10 maybe antidepressants that are sedating. These
 11 factors are quite relevant in itself and have
 12 independent risk factors.
 13 So when you're talking about, then, which
 14 patients would be tapered, I'm very concerned about
 15 them taking these highest risk patients to actually
 16 taper them because many of them really need to not
 17 be tapered, but need to be switched over to
 18 opioid-use disorder treatment with MAT [ph],
 19 because if you taper those, those are at risk for
 20 opioids, but they are probably at an even higher
 21 risk when do you taper them inappropriately fast.
 22 That brings me to my last point -- and I

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1 very much appreciate you showing Beth Darnall's
 2 study and the Stanford group about the
 3 patient-centered tapering, is that we feel we need
 4 to know what the patients actually want to do. If
 5 you do a study and you're doing something about
 6 opioid-dose reduction, you need to know where is
 7 the patient? Is this patient motivated to come off
 8 opioids? Is this patient confident that if you do
 9 an opioid-dose reduction that they will be
 10 successful in managing their pain?
 11 So these are factors you need to analyze and
 12 need to know from the patient as you make your
 13 treatment decisions, or as you your studies and try
 14 to see what's going to be my outcome. So I think
 15 you need to have information about where the
 16 patients are in this continuum of care, and you
 17 need to be very individualized as a clinical
 18 recommendation what you do with that.
 19 DR. RATHMELL: Ian?
 20 DR. GILRON: Sure, thanks. Ian Gilron from
 21 Queen's University in Canada, where the opioid
 22 crisis is also alive and well. Thank you,

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1 everybody, for excellent talks. I think we're
 2 supposed to make recommendations about clinical
 3 trials in acute chronic pain, so my one question
 4 is, should we be recommending any clinical trials
 5 where opioid consumption is the primary outcome?
 6 And if there are any situations like that, what
 7 would that look like?
 8 DR. RATHMELL: Shannon, do you want to take
 9 a stab at that?
 10 DR. SMITH: To me, I think that missed the
 11 whole picture. I think if we just look at opioid
 12 dosage, it doesn't include things like pain or
 13 functional outcomes. So it's hard for me to see
 14 that as being a valuable endpoint in and of itself.
 15 I don't know. Do you have thoughts on
 16 whether or not that's valuable, Ian?
 17 DR. GILRON: Well, since you said that,
 18 should we say that we do not recommend opioid
 19 consumption being a primary outcome? I suppose a
 20 co-primary could be something we could consider,
 21 but, yeah. It wasn't a trick question. I just
 22 want to know how we're going to articulate that in

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1 the recommendations.
 2 DR. RATHMELL: I chose Shannon because she
 3 went through all the literature that shows we
 4 focused on opioid consumption, and we really don't
 5 know that there's any clinically meaningful outcome
 6 associated with -- that's the crux of the matter.
 7 DR. GILRON: And to be fair, because, yeah,
 8 you didn't really comment on some of the quality of
 9 some of the studies. Sometimes we know from other
 10 ACTTION-IMPACT studies, there's some harkening and
 11 some mischief going on, and sometimes it's the only
 12 positive p-value that comes out, and it ends up
 13 getting articulated as a primary outcome. So
 14 certainly, we're not racing to that bottom. The
 15 question is, should we say a little more forcefully
 16 that we don't recommend a sole primary outcome?
 17 DR. RATHMELL: That's probably one we should
 18 park. It's on the record, right? Is reduction in
 19 opioid dose alone, as a primary outcome measure,
 20 either acute or chronic, viable in studies going
 21 forward? And we ought to come back to that
 22 tomorrow.

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1 Bob, is that a reasonable thing to try and
 2 come back to as we conclude tomorrow?
 3 DR. MARKMAN: I just would give you my own
 4 two cents. I think it's all contextual. For me,
 5 there's a legacy population of patients who are
 6 still marooned on high-dose opioids. They're not
 7 that many, but they're still out there; they're
 8 here and there; or people who get stuck after
 9 surgery and can't come back down. Mostly I think
 10 in that population, they're extremely motivated to
 11 come off but they're definitely afraid of
 12 re-experiencing opioid withdrawal, and they often
 13 confound their opioid withdrawal with either a
 14 worsening of the underlying pain problem or
 15 something else.
 16 I do think in that population of patients,
 17 that's where buprenorphine is uniquely valuable and
 18 another drug like buprenorphine that also functions
 19 in that way. It's just a tool to get patients
 20 through that moment of utter fear of withdrawal.
 21 And once they go to the other side, there are so
 22 many patients who do feel better. They just don't

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1 want to go back into withdrawal. Just like
 2 someone who has a primary substance abuse problem,
 3 a lot of what they're doing is trying to attenuate
 4 the intensity of that withdrawal episode.
 5 DR. GILRON: But if you did a trial of
 6 buprenorphine for transition, what would the
 7 primary outcome be? By design, your
 8 pre-buprenorphine opioid would go down to zero.
 9 DR. MARKMAN: So you're saying it may be a
 10 binary thing where you're on or off.
 11 DR. GILRON: I can't see that being a
 12 primary outcome because if you're doing a study of
 13 buprenorphine, like transition to buprenorphine,
 14 they would just come off their previous opioid.
 15 DR. MARKMAN: And then they taper off
 16 buprenorphine. I mean, that's typically what
 17 happens is -- it's been my experience that almost
 18 40 percent of our patients who transitioned to
 19 buprenorphine, because of the kinetics of
 20 buprenorphine, just like we talked about PK before,
 21 can gradually step down their buprenorphine in a
 22 way, which is much more feasible than trying to

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1 come off a premier [ph] opioid agonist.
 2 DR. GILRON: So I guess the question is, if
 3 we did a trial like that, I guess what would the
 4 design be and what would the primary outcome be?
 5 DR. MARKMAN: Again, I think you could look
 6 at either abstinence at a certain time point, or
 7 being off opioids and compare that with pain,
 8 looking at pain intensity as a secondary,
 9 potentially.
 10 DR. SMITH: Does buprenorphine have a
 11 morphine equivalence? So could you use that? I
 12 don't know.
 13 DR. MARKMAN: Some of us, there are rules of
 14 thumb that folks use, depending on the primary
 15 indication. But yes, certainly an oxycodone
 16 equivalence that folks use the community.
 17 DR. SMITH: So then you could use opioid
 18 sparing as one of the outcomes if you were doing a
 19 switch to buprenorphine study --
 20 DR. MARKMAN: Based on that conversion.
 21 DR. SMITH: Yeah. That's what I'm saying,
 22 yeah.

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1 DR. MARKMAN: And that's been done, I think.
 2 I think Nat's been involved a little bit with that,
 3 too, with Belbuca, right? I think there was some of
 4 that around Belbuca. I think there was some of
 5 that around Belbuca and the development of that
 6 program, because obviously in that clinical
 7 context, you had to transition patients who were on
 8 another opioid to buckle buprenorphine. Dr. Rauck
 9 and also others were involved in this. And I think
 10 there was a lot of analysis about that transition
 11 from another morphine equivalent to buprenorphine
 12 in that study.
 13 DR. RATHMELL: Srimi, do you want one more
 14 comment? And then we'll go on to --
 15 DR. RAJA: Yeah. I just want to make a
 16 common -- or a question for discussion because
 17 there are a lot of acute pain, perioperative pain
 18 experts here. If you're looking at the issue of
 19 opioid-use disorder in patients given prescriptions
 20 after surgery, would the duration of these
 21 prescriptions be a factor that we should be looking
 22 at in the design of the study? And if so, what

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1 should be -- there seems to be at least suggestions
 2 from the epidemiological literature that how long
 3 these patients get after surgery makes an important
 4 difference.
 5 So should this be an outcome measure that
 6 should be studied in acute perioperative studies?
 7 It's just a question for some of the experts, maybe
 8 for you as well as well, Brett, and some of the
 9 experts that are here.
 10 DR. RATHMELL: I want to give Michael a
 11 chance.
 12 DR. OSHINSKY: Thanks. I just wanted to go
 13 back to a previous comment that was made, that
 14 sponsors are interested in funding studies that are
 15 more than a year long.
 16 This is Michael Oshinsky from NIH,
 17 specifically from NINDS, which is the National
 18 Institute of Neurological Disorders and Stroke.
 19 Our typical grants that we give out are 5-year
 20 grants, which definitely allows for tracking the
 21 patient for more than a year. And from my
 22 perspective of looking at literally every single

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1 pain grant that comes into NINDS for the last
 2 4 years, there's a dearth of applications, that are
 3 specifically clinical trials, that are addressing
 4 fundamental questions to change clinical practice.
 5 The vast majority of them that come in are,
 6 does this work or does it not work with novel
 7 treatments or even -- to be honest with you, not
 8 novel treatments. And those do not do well in
 9 review. But really fundamental, strong, scientific
 10 questions that require long-term follow-up with the
 11 patients, et cetera, we know that's what NIH is
 12 designed for, those types of trials. We know that
 13 private sponsors don't sponsor those.
 14 So those fundamental scientific questions
 15 are the type of the ones that do well in review.
 16 So this is just a public service announcement.
 17 (Laughter.)
 18 DR. OSHINSKY: No, no, no. You'll see what
 19 I'm saying. If you have an idea, a scientific
 20 idea, do not dismiss as being not something NIH is
 21 interested in without contacting somebody from the
 22 program staff. It's just so many times I've heard

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1 people say I had this idea 10 years ago to do X,
 2 but I didn't think NIH would ever be interested in
 3 it. And they're really good scientific questions.
 4 So please reach out to the program staff and
 5 vet your ideas, because we have lots of different
 6 mechanisms to support the fundamental questions
 7 that you guys are bringing up at this meeting.
 8 DR. RATHMELL: And now a question from one
 9 of our short-term sponsors.
 10 (Laughter.)
 11 DR. STEINER: I'll be really quick again.
 12 Deb Steiner again. I just wanted to mention that
 13 when I first brought up this meeting to Biogen
 14 group, and I was all excited, and I'm like this
 15 sounds great, I kind of just got these blank
 16 stares, like what are we going to do with this?
 17 So not that I'm endorsing looking literally
 18 at opioid use as a measure, but just from the
 19 vantage point of if one of the outcomes of this
 20 meeting is to be able to come up with things, which
 21 not only will be utilized by sponsors but would
 22 partly be, I'm thinking about how are some of these

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1 measures going to be used because the thought is,
 2 what are we going to get on the label; how are we
 3 going to get payer reimbursement? So that's all.
 4 Thank you.
 5 DR. RATHMELL: So get real esoteric and
 6 don't get too esoteric. I got it, but be
 7 practical.
 8 TJ?
 9 DR. GAN: This is just a question to Denham.
 10 I think you are the only one that hasn't spoken on
 11 this panel yet, but can I ask you a question? TJ
 12 Gan from Stony Brook.
 13 You had showed the combination of opioids
 14 and promethazine, and that promethazine does not
 15 increase a risk of opioid suppression or breathing.
 16 And at the same time, you showed it's quite
 17 different between promethazine and
 18 prochlorperazine. Why is that such a big
 19 difference given that both has MT [ph]
 20 dopaminergic? That is one question. The second
 21 is, once you add benzodiazepines, that risk of
 22 respiratory depression goes up substantially on

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1 both sedatives.
 2 Can you address those two questions?
 3 DR. WARD: It really wasn't -- and I was
 4 probably a little confusing in my talk. But as far
 5 as the centrally acting chlorpromazine, phenergan,
 6 any of that group, they do very little to
 7 potentiate the hypercapnic depression of the
 8 opioids. But they both are dopaminergic
 9 antagonists, D2 receptors, and the carotid body has
 10 D2 receptors. And blocking a D2 receptor in a
 11 carotid body increases the hypoxic response. The
 12 dopaminergic receptor and the carotid body inhibits
 13 the hypoxic response.
 14 So for one of them, I didn't give
 15 you -- they didn't measure the hypoxic response.
 16 They just showed there was no difference in the
 17 hypercapnic response. The other study measured
 18 both the hypercapnic and didn't find any
 19 difference. Also, the hypoxic response showed an
 20 increase, a stimulatory effect.
 21 Droperidol does the same thing. Droperidol
 22 increases the hypoxic response, and therein lies

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1 the difference between those and the benzos,
 2 although obviously completely different receptors,
 3 but the GABA receptor is always an inhibitory
 4 receptor. So the benzodiazepines at the GABA
 5 receptor are going to cause central depression, and
 6 probably be removing the wakefulness drive more
 7 than an actual effect on the chemosensitive drive
 8 themselves. Benzos by themselves almost have no
 9 respiratory effect. Benzos plus opioids have a
 10 large respiratory effect, again, probably because
 11 of removing the wakefulness drive.
 12 So really combining two things, you've lost
 13 the metabolic hypercapnic chemoreceptor drive
 14 because of the opioid, and you've lost the
 15 wakefulness drive because of the benzo, and you're
 16 not left with much drive, so you get pronounced
 17 respiratory depression.
 18 DR. RAJA: So sedation really is not the
 19 problem. It's the other aspect. We comment and
 20 say it's because of sedation, which is really not
 21 quite --
 22 DR. WARD: Right.

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1 DR. RAJA: -- accurate.
 2 DR. WARD: That would be correct.
 3 DR. RATHMELL: Ajay, and then Jennifer.
 4 DR. WASAN: Hi. I'm Ajay Wasan from the
 5 University of Pittsburgh. I have two quick
 6 comments that maybe the panel can react to, and
 7 then Dr. Fields had a comment, and then
 8 Dr. Haythornthwaite had comments as well.
 9 First of all, I think a lot of the tone that
 10 we've heard so far has been, I wouldn't say
 11 negative, but this idea that we don't have good
 12 enough data to make good enough research
 13 recommendations in a paper. But it seems to me
 14 that we actually have a lot of reason for
 15 positivity here because we're hearing about a lot
 16 of possible outcome measures, which seem relevant,
 17 and a lot of possible designs to get at those
 18 questions, too. So I think that would be important
 19 to emphasize going forward.
 20 The second thing is, one thing we haven't
 21 brought up or talked about that I think is relevant
 22 is this idea of whether there are proxy measures of

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1 opioid sparing that we should consider. So for
 2 instance, if you do a study that would decrease a
 3 risk factor for prolonged opioid use -- so it could
 4 be neuropathic pain symptoms; it could be sleep
 5 symptoms; it could be psychological
 6 symptoms -- would that be considered in this vein
 7 of opioid sparing, meaning to be a valid and
 8 reasonable opioid-sparing design? So something to
 9 think about.
 10 DR. RATHMELL: Howard, would you say your
 11 name?
 12 DR. FIELDS: Howard Fields, University of
 13 California, San Francisco. Just a general comment,
 14 there's a lot of variability from patient to
 15 patient in the dose that would be required for them
 16 to have an analgesic effect. These adverse effects
 17 also have a dose-response relationship. We saw
 18 that. I think John's comparison of fentanyl with
 19 buprenorphine was a great example. That's going to
 20 be different for each side effect.
 21 So maybe a way to think about this is
 22 instead of opioid sparing, maybe it would be better

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1 to talk about dose optimization and think about a
 2 thing called a therapeutic window, which you want
 3 to optimize. So the thrust being, what we want to
 4 do is we want to better manage pain.
 5 So the Stanford study, one of the reasons
 6 that I thought it was so cool was that they were
 7 actually able to show that some people did at least
 8 as well with a much lower dose of an opioid, which
 9 meant that the dose they were taking was higher
 10 than they needed. They called it a taper, but they
 11 were optimizing the dose. So it might help us
 12 around a lot of these semantic puzzles that Nat
 13 brought up earlier in the day, don't call it opioid
 14 sparing because that's going to mean different
 15 things to different people. Call it dose
 16 optimization, then the idea is it's patient
 17 centered, and it's what we're interested, the best
 18 pain control with the lowest number of side
 19 effects.
 20 DR. RATHMELL: Or the lowest effective dose.
 21 DR. FIELDS: Or lowest effective dose, which
 22 is the best way to use them.

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1 DR. RATHMELL: Jennifer?
 2 DR. HAYTHORNTHWAITE: So that actually
 3 crosses over with the point I was going to make.
 4 And I just keep hearing there's so many important
 5 subgroups. Sorry. This is Jennifer
 6 Haythornthwaite from Johns Hopkins.
 7 DR. RATHMELL: I was going to add that at
 8 the end.
 9 (Laughter.)
 10 DR. HAYTHORNTHWAITE: Thank you.
 11 DR. RATHMELL: I'm tired of doing it at the
 12 beginning.
 13 (Laughter.)
 14 DR. HAYTHORNTHWAITE: There are so many
 15 different subgroups that we're talking about, so
 16 the VA, if they have a mental health disorder, or
 17 if there's a kind of a co-occurring medicine like a
 18 sedative. It seems to me that we want to not only
 19 think about acute versus chronic pain, but we want
 20 to think about the clinical context of the patient.
 21 So off treatment optimization also brings
 22 in, what if you have patients that are high risk

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1 for opioid-use disorder? Treatment optimization is
 2 not just about pain and side effects; it's
 3 long-term opioid risk, so that we really start to
 4 think not as just these two acute versus chronic
 5 subgroups or clinical context, but we think of
 6 within each of those, there are other important
 7 subgroups that we start identifying from the get-go
 8 in terms of in need of possibly more research, but
 9 definitely I think there are clearly subgroups that
 10 could go into clinical trials.
 11 The issue with the Darnall study that's
 12 really important, and we find this with behavioral
 13 studies all the time, we don't know who steps up to
 14 the plate in volunteers. We can't characterize
 15 them. We just know who comes, and we know that
 16 they're willing to do the study. But we don't have
 17 really good characterizations of their motivations.
 18 And you know that there are lots of reasons why
 19 people don't show up for the taper study as well as
 20 the behavioral study, but we don't have a way
 21 of -- and we need to start operationalizing those
 22 really important characteristics of the subgroups

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1 that we know are part of the patients.
 2 DR. RATHMELL: Imagine an acute pain study,
 3 even a simple acute pain study where you took
 4 all-comers, and you actually characterized those
 5 who enrolled, those who didn't enroll, and what the
 6 reasons for that were, and then follow them
 7 longitudinally. That's just not something that
 8 we've done to date. Right? It's difficult.
 9 DR. HAYTHORNTHWAITE: Yeah. And when you
 10 get to chronic pain, it's even harder. So let's
 11 say you have somebody in care with a provider like
 12 John who's willing to hold their opioid dose
 13 stable. Well, how motivated are they, given that
 14 relationship and the conversation they've had, to
 15 sign up for a tapering study?
 16 So if you're just interested in opioid
 17 sparing, you're not going to engage people in the
 18 same way. So the whole idea of maximizing dosing
 19 might be a perfect way around --
 20 MALE VOICE: Optimizing.
 21 DR. HAYTHORNTHWAITE: -- sorry, optimizing,
 22 not maximizing.

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1 (Laughter.)
 2 DR. RATHMELL: I think you said minimizing
 3 dose.
 4 DR. HAYTHORNTHWAITE: Big mistake.
 5 DR. RATHMELL: Lowest effective dose.
 6 Michael? Who are you?
 7 DR. ROWBOTHAM: Michael Rowbotham, Sutter
 8 Health and UCSF. Just one comment since there are
 9 so many clinicians on the panel right now, that
 10 John brought up about the fear of pushing the
 11 button on Epic screen. Physicians are all being
 12 tracked as to how much opioid they're prescribing.
 13 And absolutely, you're being tracked by whatever
 14 healthcare system you're working in. You're being
 15 tracked on various state and national pharmacy
 16 databases. And the reason why academic pain
 17 clinics see such a high proportion of what you call
 18 opioid refugees, which is a good term, is that
 19 you're the only ones that can get away with
 20 prescribing without sanctioned scrutiny and
 21 unpleasant interactions with your chief medical
 22 exec, wherever your physician practice is.

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1 So it's a real issue, this stigmatization.
 2 And I've had health insurance companies come to me
 3 and literally, they will have the charts on all the
 4 patients who are, let's say, over 300 morphine
 5 equivalents per day. They know all of them and are
 6 tracking how they're being managed.
 7 So even though we may discount that as an
 8 outcome measure, that's what the insurers and the
 9 healthcare systems are often looking at. They
 10 don't care about anything else except number of
 11 prescriptions and MEQs.
 12 DR. RATHMELL: Yeah, but honestly, from our
 13 own local experience, we see in our own ranks huge
 14 disparities amongst the chronic pain physicians.
 15 So what else would you do as an insurer when you
 16 say you all have the same subspecialty designation,
 17 and yet we've got this same -- "What the heck is
 18 going on here? You're seeing the same group of
 19 patients, aren't you?" That's what they're saying
 20 to us.
 21 So we need to have some common philosophy,
 22 and that's my feeling, at least within a single

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1 clinic because, otherwise, the patient who comes on
 2 Monday, they get one treatment. They come on
 3 Friday; they got a completely different treatment,
 4 in the same clinic and the same health care, and it
 5 drives practitioners crazy, and patients,
 6 obviously.
 7 Please?
 8 DR. JAMISON: John, a good part of
 9 your -- oh, I'm sorry.
 10 DR. RATHMELL: No, that's good. I'm going
 11 to keep going.
 12 DR. JAMISON: Bob Jamison Brigham and
 13 Women's Hospital, Boston. I think I can't wait to
 14 read this paper when it comes out.
 15 (Laughter.)
 16 DR. JAMISON: The memorable part of your
 17 talk, John, is the individual differences, and it
 18 reminds us, every once in a while, we're dealing
 19 with a lot of different people, and how do you
 20 track that? So how do you come up with guidelines
 21 that are going to be for everybody, recognizing
 22 there are huge individual differences?

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1 Something that may come up tomorrow -- I
 2 appreciate any of your thoughts on this today, but
 3 how do we use innovative technology to track people
 4 better than what we have right now to help us
 5 understand how people are using opioids, and then
 6 how does that help make decision-making? So we're
 7 talking about activity monitors, we're talking
 8 apps, we're talking about a lot of the things that
 9 are out there now that are futuristic, but they're
 10 available.
 11 So I'd be curious of anybody's reaction to
 12 that in terms of how we really understand
 13 individual differences in response to opioid use.
 14 DR. RATHMELL: There's an app for that.
 15 (Laughter.)
 16 DR. RATHMELL: Anybody want to comment on
 17 using these?
 18 DR. STACEY: I'll make a quick comment.
 19 There is going to be lots of great options I think
 20 for that, ranging from the Smart Bottle that
 21 opens -- every time it's open, it tracks. Then you
 22 have it hooked up with an activity tracker. So the

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1 patient opens the bottle, takes a pill, then they
 2 go sit on the couch; or they open the bottle, take
 3 the pill, and then go out and does the yard work.
 4 Those are very different outcomes, and you can
 5 track that.
 6 There's also some talk for select chronic
 7 pain patients and an intensive study that would
 8 require deep pockets of basically wiring their home
 9 to track each time a door's open, so you can track
 10 their movements within their home, when they leave
 11 the home, that kind of stuff, to look at their
 12 activity levels to associate with it. There are
 13 ways of looking at -- even just with a fitness
 14 monitor -- there are a whole bunch of things you
 15 can do, and I think we really don't explore those
 16 things very much.
 17 I'm sitting here listening to this
 18 conversation and thinking if I'm in drug
 19 development, boy, what drug am I going to come up
 20 with that's going to really be the one for chronic
 21 pain opioid-dose reduction. I don't think anybody
 22 is like really burning with that. It just shows a

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1 big separation between the acute world and the
 2 chronic world. And also, Jennifer's point about
 3 the subsets, about the differences, how different
 4 the patients are, and we need to really look at
 5 these different types of patient populations.
 6 I ask patients really simple questions like,
 7 "Do you read?" I don't suggest Beth Darnall's book
 8 about tapering opioids if they don't read. So
 9 there's like really simple things that kind of
 10 separate people out, like what do you do for fun?
 11 There are a bunch of things that help separate
 12 things out that are not ever going to be in a
 13 clinical trial.
 14 DR. RATHMELL: John, you want to comment
 15 quickly? And there's one last question.
 16 DR. MARKMAN: I'll be a little bit of a
 17 passive monitoring Luddite. I will tell you -- and
 18 the reason why I think -- I think that the history
 19 and the narrative are the most important part when
 20 it comes to pain probably because of what John
 21 Farrar said, is because we don't have another tool.
 22 To me, all of these reductions, how much you moved,

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1 or how many times you opened the bottle, I'm just
 2 worried that those get over-interpreted in a way,
 3 that self-report -- they just don't have the
 4 richness of self-report and give you the context.
 5 I always feel -- I think those are great
 6 adjuncts to the self-report, but I truly fear the
 7 world where we take away someone's opioid because
 8 they haven't walked enough. And we don't really
 9 understand why they haven't walked. Maybe they
 10 also have vertigo. So my concern about all the
 11 passive monitoring -- and my own institution is
 12 really enamored of this -- is the fact that unless
 13 it's coupled with a PRO, I just feel like it's very
 14 hard to interpret.
 15 DR. RATHMELL: Last question?
 16 DR. C. BROWN: I had a comment on --
 17 DR. RATHMELL: Sorry. Just say --
 18 DR. C. BROWN: Cole Brown, Innocoll. I had
 19 a comment on two statements that were made earlier.
 20 One was the question posed around utilizing opioid
 21 sparing as a primary outcome. I just wanted to
 22 orient regarding the clinical development of an

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1 acute postoperative analgesic. I think if I'm
 2 developing a drug for postoperative pain, I think
 3 primarily what I'm going to need to prove is that
 4 it does reduce pain intensity.
 5 So the second aspect is important, that
 6 opioid sparing is very, very important, so
 7 considering it as a co-primary. But as developing
 8 an analgesic, I think I need to demonstrate that it
 9 decreases pain intensity first and foremost.
 10 Then a second comment was regarding to
 11 following opioid sparing for a longer time period.
 12 I think that's interesting, and one I guess concern
 13 that I would like to pose to the group is, yes,
 14 there is a good amount of data showing that if you
 15 can decrease the severity of pain intensity in that
 16 initial acute postoperative period, that perhaps
 17 you are decreasing the pain intensity further down
 18 the line. But on let's say day 6 or 7, the assay
 19 sensitivity, that delta between the drug I'm
 20 developing and placebo is really decreasing, so I'm
 21 not really going to be able to show that
 22 difference. So we're maybe losing that if we

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1 follow it for a longer period of time is my only
 2 concern.
 3 DR. RATHMELL: And a very reasonable
 4 concern. But what if that initial difference
 5 between the new drug and conventional analgesics
 6 looked at 6 months later and, even though you only
 7 use the drug for 7 days, actually changed something
 8 about drug use habits 6 months down the road in
 9 patients who may have had persistent opioid use?
 10 That's the kind of maybe it will, maybe it won't.
 11 Anyway, I want to thank everybody for all
 12 their input here. Any words of wisdom from our
 13 organizers?
 14 (Applause.)
 15 Adjournment
 16 DR. RATHMELL: So dinner is at 7:00, and
 17 it's in the room where we've had all of our meals
 18 thus far.
 19 (Whereupon, at 5:32 p.m., the meeting was
 20 adjourned.)
 21
 22

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