ACTTION-APS-AAPM
Pain Taxonomy (AAAPT) for Acute Pain

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ACTTION

Developing the Framework for a
Comprehensive and Evidence-Based ACTTION-APS-AAPM
Pain Taxonomy (AAAPT) for Acute Pain

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8:07 a.m. to 4:51 p.m.

Sofitel Washington DC
Lafayette Square

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:07 a.m.)

Welcome and Introductions

DR. TURK: Good morning. Please take your seats so we can get started. Thank you.

My name is Dennis Turk, and I am happy to have all of you here at the AAAPT meeting. And I will formally introduce things in a moment, but let me just get started with a couple of housekeeping slides, make sure everybody -- there will be coffee around, so you can get up and get coffee if you want to. There will be plenty of coffee breaks for you to do that.

Okay, so let's just do a little bit of housekeeping. Now, you probably don't want me reading all this to you. You can read it yourself, and you know most of these things. The only thing I'll emphasize is the restrooms, which we always get asked to, out the door to the left, next left, through double doors, and you'll find them. So those are always the important things.

Standing in the back, with the blue top, is

Page 5

Valerie Thompson. She and Andrea Speckin are the organizers of this meeting. They can help you and handle all details that you bump into as far as your room or your flights, or anything of that kind, any questions you have. They are our saviors and have been with us, Bob Dworkin and myself, for a long time, so we count on them to really keep things going, so any questions you have.

The speakers, if you have any slides, the gentleman in the pink shirt, my left, will be happy to help you set those up if you haven't already given them to them as well.

So let's just make sure you've had a chance to look over the housekeeping. Nothing particularly unusual. We already heard that it's a bit warm in here, so we're taking care of that. The microphones are the types you have to push the button on. They're not voice activated. And if one person is speaking, obviously you won't be able to get in there. It will light up red when you do it, and then you turn it off or it goes off on its own.

Page 6

Okay. So let me introduce the welcomers for you. This meeting, as you may know, is a joint collaboration with the ACTTION public-private partnership, which I'll tell you more about during my formal presentation, and the American Pain Society and the American Academy of Pain Medicine. And that is, we're bringing these organizations all together with our real objective, which is to get accomplished at this meeting, and you'll hear more about that.

But I want to welcome our two welcomers. First Dr. Dan Carr from Tufts University, the president of the American Academy of Pain Medicine.

Are you president or president-elect?

DR. CARR: President.

DR. TURK: You're president. Okay, Dan. And then when you're done, we'll introduce Greg, and then back to me.

DR. CARR: Thank you very much, Dennis. And I have to reflect personally that I had the privilege to be at the first couple of IMMPACT meetings that really produced very high impact

Page 7

papers that have been widely cited, and I feel very proud to have maintained that relationship over the years. And I think Bob and Dennis, we'll have a spontaneous round of applause to thank the two of them.

(Applause.)

DR. CARR: Sorry. That wasn't on the schedule, but I just lost control of myself.

So I also want to thank everyone in this room. It is a dream team of people who are incredibly and uniquely well informed, both about issues relating to taxonomy, the structure of ACTTION and AAPT, and also acute pain. So this is an amazing group.

I think I have to give a special thanks to Henrik Kehlet for distance travelled, although Steve Stanos, and John, and Greg and the Washington contingent might equal the thousands of miles of travel. But it is just a fantastic group of people.

So could I have the first slide?

Hmm, is that my first slide? It looks like

Page 8

a harbinger of something. In any case -- oh, the boxes didn't project. But this is what we're here to do. We're here to develop a framework for a comprehensive and evidence-based ACTTION-APS-AAPM pain taxonomy for acute pain.

Acute pain. Now, for some of the people in this room, acute pain never stopped being important, and they contributed and made advances in practice. But I would say that at the present time, we can look back over the last 15 or 20 years and look at an interval where the period of acute pain didn't seem to be that interesting.

I'd say it might have been viewed as a mechanical thing, as a quality, internal quality assurance thing. But I'd say that it's been very gratifying to see in the last handful of years a true resurgence of interest and NIH funding for acute pain.

I'm going to quote a position paper, a survey of the state of acute pain that was first authored by Patrick Tighe, who is one of people here today, but also included Mike Kent and Trip

Page 9

Buckenmaier, and several other people from AAPM. And this survey said, well it looks like there is resurgent interest, and this began around the 2010s.

For one thing, the application of multimodal therapies and enhanced recovery after surgery has been increasingly the norm. It saves money, it allows people out of the hospital more quickly. And we now have effective, proven, multimodal regimens to accomplish that. They're not perfect. They don't work for everybody equally. But they're reliable enough that the treatment of acute pain has become integrated into the fabric of daily care.

By doing so, looking back historically, using multimodal regimens, assessing pain, titrating pain treatments to pain scores, and so on, there's been a demonstrable reduction in adverse events. There is also a likely reduction in the chronification of acute pain and also costs.

Of course, there's increased patient satisfaction, and I guess personally I don't know

Page 10

how many of you are following what's going on in the U.S., but there's controversy about even asking questions about pain. Be that as it may, I think just sitting here in this room, most of us would agree that if patients are happier, that's a good thing.

So here are the hypotheses that I would see driving this meeting. First of all, the hypothesis is there's an opportunity to advance acute pain research, and I think practice, by revisiting the taxonomy of acute pain from an inter and multidisciplinary perspective. And we certainly have assembled the right people to do that.

The next hypothesis is that the recent and ongoing experience with the taxonomy of chronic pain under the AAPT aegis can guide the process for acute pain. And third, the chronic pain process, the AAPT process, may not be perfectly generalizable to acute pain, so we have to work out a few things about that.

I've reviewed the slides that people submitted, and thank those of you who did so, so I

Page 11

know that this is duplicative. But this will also serve a little bit as an introduction to the first speaker's talk, namely by Roger Fillingim, in that earlier and ongoing process, there were five key dimensions that were identified of relevance to taxonomy.

In particular, there were core diagnostic criteria that allowed one to define or decide if a certain condition were present. And I'll speak to this later in my longer talk, but I think there's a little bit more emphasis on diagnosis in the chronic pain effort than there is in the acute pain effort where the cause is often very clear.

Also, there are common, and by common it's really meant frequent features of that condition, so there are additional characteristics and non-pain features: common medical comorbidities that co-occur with high frequency, consequences in the neurological, psychobiological, and function, such as sleep, and then putative neurobiological and psychosocial mechanisms, risk factors, and protective factors.

Page 12

So you'll see this way of thinking. This is a way of organizing one's thought about the taxonomy, and I'm sure Roger will touch upon that.

I'll throw out some ideas, the purpose, in this few minutes of introductory remarks, not to gender debate about this. But if I go back and look at that Tighe, et al. acute pain medicine shared interest group paper, their working definition of acute pain was, " the physiologic response and experience to not just stimuli that can become pathologic, is normally sudden at onset, time limited, and motivates behaviors to avoid actual or potential tissue injuries."

In that same state of acute pain paper, it was pointed out that the experience of acute pain, as we think about it, generally has an exciting event, it's of sudden onset, it's time limited, and has the potential to develop into a pathologic condition.

So I'm throwing these out not to debate them per se, but to kind of begin to have us get our heads around two traditionally distinct constructs,

Page 13

the one construct being chronic pain, it's long established, you don't have the opportunity to intervene at the beginning because the patient comes to you long after the beginning; then you have acute pain, it's a somewhat different context, and I'll go into that in a longer talk.

I read with great interest the initial publication from the AAPT effort, which was first authored by Roger. And I, for the purposes of this meeting, wanted to call to your attention one portion of this, which said that, in considering the approach to take, whether to take an evolutionary approach or revolutionary approach, they said, and Roger wrote, that a revolutionary approach to chronic pain taxonomy might completely abandon current diagnostic labels and approaches based on anatomical structures and organ systems in favor of an approach that prioritizes the neurobiological mechanisms underlying chronic pain.

I think we'll hear a great talk. I've had a sneak preview of Tim Brennan's slides, and I think you'll be well informed by his talk.

Page 14

But having weighed whether to do an evolutionary or revolutionary way forward, they decided I think to pull back a little because there was inadequate knowledge of mechanisms. The area was just not there yet to support this revolutionary approach.

Also, ultimately, these products need to have some impact on the real world. And Roger wrote that, "Clinicians and scientists comfort with classical systems and the reluctance to change tipped the balance back towards an evolutionary approach."

Now, I am a member, or I should say survivor, of the IASP task force on taxonomy. And as a young faculty person, coming into the task force was an experience I will never forget in my lifetime because the heat and passion of battle, even sustained over internet, was staggering to me, that people could be so passionate.

I think ultimately -- I may not be doing this justice, John, but I think it's not inaccurate to say that ultimately the entire task force was

Page 15

fired because they did nothing but fight, or the amount of productivity relative to the amount of fighting was viewed as too low, so it was reconstituted.

This also being the week of Passover, I thought, well, we can't actually have services here, but I came across this quote from the wonderful scholar Maimonides, and we're looking about over 800 years ago. And in one of his writings on Judges, which is a tremendous thing to read in terms of conflict of interest and so on, very modern, he had this thought that, "Two scholars who dislike each other are forbidden to sit together in judgment for this might lead to the rendering of a perverted judgment. Prompted by hostility, each will be inclined to refute the arguments of the other."

So who knew that he served on committees?

(Laughter.)

DR. CARR: Who knew that he was a member of the task force on taxonomy? But I think we're really in good shape because we have a very

Page 16

congenial and positive group of people here.

Actually, I see Rob Hurley in the back, and I didn't mean to leave you out from the acute pain effort.

But we are benefiting by a great group. We're benefiting by a formula that's been worked out. It's an amazing formula that Bob and Dennis have worked out over the years. I guarantee this will produce something, and the question is how much and how extensive, and that depends upon all of you.

So I'm going to turn the podium over to my colleague, Greg Terman, and thank you for being here and traveling here.

DR. TERMAN: Good morning. I don't have any slides, but I didn't want to pass up an opportunity to welcome you and thank you for being here on behalf of the American Pain Society for this collaborative meeting.

Discussing development of framework for acute pain taxonomy, I think it's very timely. Some of you may have read on blogs or in the papers

Page 17

about the recent CDC guidelines and people describing, with satisfaction or with horror, the acute pain part of those guidelines, and probably not having read the fine print, which says it isn't concerning the traumatic or perioperative acute pain, which is, really, most of the patients that I've taken care of over the last close to three decades of being an acute pain doc.

So I think this is a great opportunity. I'm pleased to say that the American Pain Society is becoming more and more interested in acute pain, certainly based on the joint APS perioperative guidelines that were just published earlier this year.

I think that's going to continue or increase as those of you that have kind of looked or are involved in the Federal Pain Research Strategy through NIH, there's certainly a considerable portion of that effort around acute pain. So I think that's really outstanding, and certainly as an acute pain doc I find it very good.

If we're going to discuss or treat or

Page 18

research acute pain, it might be useful if we know what we're talking about. So I look forward to this meeting in terms of thinking about taxonomy of acute pain, and I thank you again for coming.

DR. TURK: Thank you, Dan and Greg. Actually, when Dan was speaking about Maimonides quote, I was remembered of a cartoon that I once saw, which basically said that the only thing two experts will agree on is that the third expert is an idiot.

(Laughter.)

DR. TURK: So perhaps we'll be able to figure something out for the group here.

Again, I'm Dennis Turk from the University of Washington, and I want to welcome all of you here from ACTTION, which stands for Analgesic, Anesthetic, Addiction, Clinical Trials, Innovations, Opportunities, and Networks. Whew! I got through that whole thing.

One of the things you're going to learn, you already heard Dan mention IMMPACT, which is another acronym that some of you may be familiar with,

Page 19

Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. Dr. Dworkin, who is the perpetrator of these acronyms, is a card-carrying member and fellow with the American Academy of Acronymnilia [ph], so therefore we're going to add yet one more acronym to the group here, and that will be the AAA -- AAAPT.

You've also heard mention about the chronic pain guideline, and you'll hear a formal presentation of that from Roger Fillingim.

But just to understand how that began, it was essentially a group like this that got together trying to see could we come to some agreement about the relative and appropriate dimensions that would be considered in a taxonomy. And bemoaning what had occurred to the original classification that Harold Merskey had created for the International Association for the Study of Pain, which was used by almost no one, if anyone -- and to my knowledge, there's only been one study that's actually tried to evaluate it. I did it. We concluded that it was totally unreliable, that raters could not use

Page 20

that system to come up with anything reliable. So bemoaning that was some of the impetus.

We did have interesting meetings. We didn't argue and scream nearly as much, I don't think, as the IASP taxonomy, but we were able to hammer some things out. And I think the manuscript that you saw gives you a wonderful idea of what we're trying to do with that.

It's expanding. There are working groups in -- what, Bob? -- 9 areas or 8 areas, that are working for specific disorders to come up with classifications that will fit within that classification.

The background papers for the AAPT taxonomy will be appearing in a supplement in Journal of Pain, which will be out probably September/October if all goes well. It will have much more detail and rationale as backup for what Roger produced in that particular paper, and really articulating much more clearly the dimension. So you can look forward to receiving that.

Let me just move ahead. This is to welcome

Page 21

you officially. I have the logos of all the relevant organizations. Consider yourself welcomed. I should say, by the way, when we were talking about the distance people came, we forgot Knox Todd, who came I think the longest -- how many miles did you come, Knox?

DR. TODD: Oh, so many miles.

DR. TURK: How many hours did it take you to get --

DR. TODD: Eighteen.

DR. TURK: Yes, I think Knox with Argentina. Yes, I think Argentina may be the furthest distance, but it definitely took the most amount of time for somebody to get here. So in addition to Henrik and anybody else that we've got here from Europe, also to thank Knox for making this long trek here.

We really did try to get people who were knowledgeable across the spectrum of acute pain areas so that we went from post-op, to visceral, to cancer, to emergency room, et cetera. And the people around the room, some of you may not know

Page 22

each other, so what I thought I would do is very quickly, and if you could do this quickly, just say who you are, where you're from, what university you're from. And let me tell you, there will be a quiz at the end, so you must stay awake and remember who you have beside you.

So Bob, why don't we start with you. They already know who you are, but go ahead.

DR. DWORKIN: Bob Dworkin, University of Rochester.

DR. TURK: Knox?

DR. TODD: Knox Todd. I was the founding chair of the Department of Emergency Medicine at the University of Texas MD Anderson Cancer Center for the last five years. In December made a career change and live in Mendoza, Argentina. And if anyone wants to come down and sample the wine or the olives, we'd be happy to have you.

DR. MACKEY: Sean Mackey, Stanford University.

DR. BUVANENDRAN: Kumar Buvanendran from Rush University Medical Center, Chicago.

Page 23

DR. KEHLET: Henrik Kehlet, Copenhagen University, Denmark.

DR. FILLINGIM: Roger Fillingim, University of Florida.

DR. RAJA: Srinivasa Raja, Johns Hopkins University in Baltimore.

DR. MCLEAN: Sam McLean. I'm an emergency physician from the University of North Carolina.

DR. SCHREIBER: Kristin Schreiber. I'm an anesthesiologist and pain researcher at Brigham and Women's Hospital in Boston.

DR. BELFER: Inna Belfer. Former University of Pittsburgh, now FDA.

MS. GORDON: I'm Deb Gordon. I'm a nurse from the University of Washington in Seattle.

DR. STACEY: I'm Brett Stacey, and I [inaudible – off mic] if I should leave. I'm also from the University of Washington and I run the [inaudible – off mic].

DR. KENT: I'm Mike Kent from Walter Reed.

DR. TIGHE: Patrick Tighe, University of Florida.

Page 24

DR. TURK: Stop for one second. Those two gentlemen right there are going to be taking the minutes, the notes from this particular meeting. They're going to be drafting up the manuscript that you're all going to be involved with. So be very kind to them and make sure that you give them good information.

I should also say, to stop right now, the slide presentation that you're going to be seeing, we've already had people ask about them, we will -- I'm not sure how long, but in a couple of weeks get these all up on the ACTTION website, so that you will be able to download these for those who are interested.

For those of you who did slides, if you have any proprietary information in any of those, let us know, and we'll make sure those don't get included. But everything else will become available to everyone, both in this room, but also anyone outside who was not able or was not invited to attend because of the space limitations.

Sorry. Okay, Trip?

Page 25

DR. BUCKENMAIER: Trip Buckenmaier, Uniformed Services University, [inaudible – off mic].
DR. POLOMANO: Rosemary Polomano, University of Pennsylvania.
DR. STANOS: Steven Stanos, Swedish Health Systems, Seattle, Washington.
DR. WEISMAN: Steve Weisman from the Medical College of Wisconsin and Children's Hospital Wisconsin.
DR. SURESH: Santhanam Suresh from Lurie Children's Hospital and Northwestern University in Chicago.
DR. WU: Chris Wu, Hopkins.
DR. BRUMMETT: Chad Brummett, University of Michigan.
DR. HURLEY: Rob Hurley, Medical College of Wisconsin and [inaudible – off mic].
DR. EDWARDS: David Edwards, Vanderbilt.
DR. SCHUMACHER: Mark Schumacher, UCSF.
DR. TURK: Jen?
DR. GEWANDTER: Jen Gewandter, University of

Page 26

Rochester.
DR. COHEN: I'm Robert Cohen. I've been at Beth Israel Deaconess Medical Center, part of Harvard Medical School, and now I'm with Analgesic Solutions.
DR. BRENNAN: Tim Brennan, University of Iowa.
DR. RAHMAN: Siamak Rahman, University of California, Los Angeles.
DR. DESJARDINS: Paul Desjardins, Rutgers and Tufts.
DR. BRUEHL: Steve Bruehl, Vanderbilt University.
DR. LOESER: John Loeser, University of Washington.
DR. SCHACHTEL: Bernie Schachtel, Yale University.
DR. TURK: Terrific. As you probably picked up, we've got a range of disciplines, a range of different areas where people come from outside the United States, within the United States. We really do have, as Dan said, a dream team.

Page 27

So consider yourself welcomed. Make sure you get a chance to interact with your colleagues. There are plenty of coffee breaks, plenty of lunch breaks, other opportunities for you to do that.
What we've learned from a number of these meetings is that the conversations and discussions that go over among those breaks actually are very useful and informative because they often then feed back to subsequent discussions. So we encourage that as much as you want to do that.
Okay. Let's go forward. What are the objectives? You heard sort of Dan do this, to review the AAPT classification -- you've heard more about that than you're probably going to want to hear -- from chronic pain, determine its appropriateness and any modifications required to extend to acute pain.
To disseminate these considerations, observations, suggestions and research agenda by publishing a peer-reviewed journal. That peer-reviewed journal will possibly be a combined publication of the Journal of Pain and Pain

Page 28

Medicine for the two organizations that are here.
This can be done -- so don't worry about the logistics, but it can come out simultaneously in two journals if the editors and the publishers are willing. So far, they've been very positive, so that shouldn't be a problem.
In order to accomplish these objectives, some herding of the participants is needed.
(Bob Dworkin nods no.)
Now, notes on the gentle art of herding, participants don't like to be herded. In fact, you can't readily -- AAPT participants, we can't get them to do much of anything, but we keep trying anyhow. Participants like to herd themselves, but you're not very good at it, so you sometimes need a little assistance.
Participants understand that they sometimes need to be herded, however, that doesn't make them any less recalcitrant or easier to herd. And harsh herding usually has negative consequences.
So that's what we've learned, and here we are, the happy team who is going to help herd you

Page 29

because we want to do this. Remember, the goal is at the end of the two days, day and three-quarters, is to have enough information available, discussing the important and relevant issues, that will then end up with Patrick and Michael in their hands to get it pulled together.

They will create a draft of the manuscript. It will be circulated to all of you, all of whom are invited, encouraged, wish to be co-authors as long as you sign off that you are willing to do that. We hope you will provide comments.

Let me explain to you about doing manuscripts with this many authors. It is difficult and slow. We appreciate, greatly appreciate, if in fact when you have a draft sent to you or some question comes to you, you respond as quickly as reasonable. Don't drag this out.

Comments like, great, thanks, are not real helpful in the early stages of a draft, so it's useful if you have comments that we can contribute to this. When we then circulate subsequent drafts, again, the faster we can turn this around, the

Page 30

better.

When we get the inevitable comments back from the journal reviewers, we tend to make the changes and address those, assuming they're relatively minor, identify those changes in usually red font on the next draft you'll see, and encourage you to pay attention specifically to the red font.

People sometimes say, oh, I forgot I didn't read this section carefully and there's something else I want to change. We prefer you not do it at that point since it's been through review, so try to stick to it. Paul is shaking his head because he's been with us as a first author, a lead author on one of these particular manuscripts. So we encourage you to do that. Okay?

So you've heard the logistics. You know what you're being asked to do. You now know all your neighbors and friends. I'm not going to do the quiz, but I will expect you to know each other. Now we do have name tags. You can understand about the housekeeping.

Page 31

So Bob, unless you have a question and you've already -- I introduced Valerie, who you saw, who we thank, and our gentleman in the back on my left who is taking care of the slides and the audio/visuals. Should speakers have any questions, talk to them.

Bob, any comments you'd like to make? Okay, then consider yourself welcomed. You gentlemen can step down, and I'll call Roger Fillingim up, who is going to be our first speaker.

Roger is a professor at the University of Florida. He has been past president of the American Pain Society, and he was most importantly the lead author of the AAPT Chronic Pain guideline.

He herded the cats. His picture is there. He was one of the key herders of the cats and was able to produce that manuscript. He can tell you stories offline, horror stories, if he wants to, about getting the cats herded. But it's my pleasure to have Roger come and sort of give you the background, which you've been sensitized to.

The manuscript was circulated. Hopefully,

Page 32

you all read that. So Roger, they're all yours.

Presentation – Roger Fillingim

DR. FILLINGIM: Thanks very much, Dennis.

My job is to just give you some background on the chronic pain taxonomy. As Dan pointed out, one of the goals is to determine the extent to which the chronic pain taxonomy can inform the AAAPT and what modifications might be needed. So I'm going to tell you about the process we went through and give you a sense of how the sausage was made.

Dennis mentioned the acronyms. If you're not aware, Bob directs a clinical research acronym program, also known as CRAP.

(Laughter.)

DR. FILLINGIM: If any of you are interested, I think it's a great resource.

(Laughter.)

DR. FILLINGIM: So this is just an overview of what I'm going to talk about today. I'll give you a brief history, talk about some of our conceptual considerations during the development,

Page 33

highlight the current framework that you've already heard a little bit about, and then talk about where AAPT is going in terms of future directions.

This is just a timeline sort of from inception to slightly past today. Dennis referred to the Journal of Pain supplement that's getting into its final stages in terms of article submissions and revisions. So we think that's going to come out in about September.

But this all started back in September of 2012 when Bob emailed me -- I was then president of APS -- and proposed this. I'll tell you a little bit more about that. And the APS board approved that shortly thereafter.

We then planned for the AAPT launch meeting, which occurred in May of 2013, so that's about three years ago, right? And then you can see the other activities from about -- so we had our second AAPT meeting in July of 2014, and since that time, the working groups, and I'll tell you about those shortly, have been developing their diagnostic criteria.

Page 34

So this is some of the text from Bob's initial email to me, and I bolded some text to give you a sense of why Bob and Dennis thought this was an important idea. But a comprehensive pain taxonomy is essential so that consistent and accurate diagnoses are used for clinical research, clinical trials, and to facilitate comparisons across studies for systematic reviews and meta-analyses. And it's also critical for regulatory reviews of new drug applications.

So that was a large part of the rationale for getting things going in the first place. I mentioned May of 2013 was our launch meeting. And our goal was to develop a framework, much like our goal here this week -- to develop a framework that all working groups could apply in developing diagnostic criteria for chronic pain conditions.

Here's essentially the agenda that we followed at that meeting. We had Chuck O'Brien, a psychiatrist who has been involved in the diagnostic and statistical manual of the American Psychiatric Association. And at that time,

Page 35

essentially, he had to leave the meeting because DSM-5 was being unveiled in California or something. So he told us a little bit about some of the history there, because we thought that the DSM process was, in some ways, a model for what we might be thinking about with chronic pain.

Then we had some discussion of chronic pain mechanisms. And then we had three presentations by individuals who had been involved in developing evidence-based diagnostic criteria and conducting research on those criteria. So that was Sam Dworkin for TMD, Eva Widestrom-Noga with spinal cord injury pain, and then Steve Bruehl, who is of course with us here today talking about complex regional pain syndrome, just to give us some ideas of the process whereby diagnostic criteria get developed and then tested.

I then talked some about, at that point, what was our thinking about how we might develop a multiaxial framework, and then there was lots of discussion. And ultimately, we developed work groups, decided on the core diagnostic criteria

Page 36

that would be part of our framework, and then talked about where we were going to go from there. So that's sort of how the meeting unfolded in a nutshell.

You've heard both me and Dennis mention this upcoming Journal of Pain supplement. The rationale for this -- and you can see a list of the articles, most of which are already accepted. A couple of them I think are in the revision phase right now. But as we think about our working groups, who are developing diagnostic criteria, we didn't want every working group to have to reiterate, here's how you should assess pain. Here's how you should assess psychosocial mechanisms.

If that happened nine times, that's a huge waste of journal space, so we wanted to give some foundational information and references that all of the working groups could refer to. And so that's the rationale for this supplement, which we hope to see later this year.

So let me dig down into the meeting a little bit and some of the things we were thinking about

Page 37

leading up to the meeting and during the AAPT meeting. Of course, we were talking about diagnostic criteria, but there are sort of overlapping and confusing terminologies that get thrown around. And in fact, we had to decide what are we calling these things. Are these chronic pain diseases, disorders, conditions, syndromes?

This comes primarily from the psychiatric literature. If you distinguish among these terms, a disorder is a medical concern, an abnormality, an aberration, and this is generally used when the pathophysiological process is not well-known.

A disease refers to a known pathological process that leads to one or more disorders. And a diagnosis is a procedure used to decide whether or not a certain disorder or disease is present in a patient. And I believe we settled on chronic pain conditions, if my memory serves, so we skipped all of these terms.

If we think about diagnosis -- I think this is relevant to our work here, and it certainly was relevant to our work in AAPT -- the purpose of

Page 38

diagnosis is to guide treatment and prognose. There are other secondary purposes to which diagnosis has been applied, but those are far less important, in my view.

So what we should be thinking about as we develop diagnostic criteria is will these criteria help us decide what treatments need to be perpetrated on these patients, and that's really the ultimate goal. And it might help us tell patients what they can expect, what the course of their condition is likely to be?

That implies that treatment is based on diagnosis. And now we know that this isn't necessarily true at present, but we would like it to be true in the future. This is one of my favorite cartoons, "We can't find anything wrong with you, so we're going to treat you for symptom deficit disorder." We never treat people until after we've diagnosed them.

So another conceptual concern is this issue of lumping versus splitting, again from the psychiatric literature, but certainly relevant to

Page 39

chronic pain. The open question is whether different diagnostic manifestations of a basic pathological process have been divided into multiple diagnostic silos creating artifactual comorbidity in certain circumstances.

So are we making distinct disorders or conditions out of something that's actually one pathological process, and that creates many comorbidities that we see?

As I say, this is relevant to chronic pain. We know we have overlapping conditions in the chronic pain space. And one of the articles coming out in the JoP supplement addresses these overlapping pain conditions. So to what extent are these actually distinct disorders versus reflections of some global underlying pathophysiology?

Another thing we wanted to keep in mind as we develop AAPT is what are the characteristics of an ideal diagnostic system? And here are some of those characteristics here. So there should be some biological plausibility, which you might

Page 40

interpret as the diagnostic system should be translatable into pathophysiological mechanisms. The diagnostic system ideally would be exhaustive, that is it allows you to characterize all of the pain conditions that might be encountered by a clinician.

The diagnostic categories should ideally be mutually exclusive so that you can tell that if a person has X, that's different from a person who has Y. Now, a given person could have both X and Y, but those would be two separate conditions.

Then of course, it should be reliable, and that requires some research to determine the reliability of the system.

As Dan alluded to, we were concerned and we opted for evolution rather than revolution because we wanted the system to be clinically useful and also useful for research. And if you take too far a leap, it's difficult to encourage people to continue using a system. And then ideally, the diagnostic system would be simple enough for people to understand and apply. So these are some of the

Page 41

principles we were shooting for in the development of AAPT.

At the time that we were contemplating development of AAPT, this was essentially the state of pain classification, and I think this is largely true still today. There are multiple diagnostic systems proposed by different groups with no uniformity of structure or approach.

Even the three presentations that we had by Sam and Eva and Steve at that time, those were completely independent initiatives. There was no guiding framework. So they did quite good work and quite good research, but in completely different spaces.

Unlike those three systems, most of the diagnostic criteria out there have very little evidence supporting their reliability or validity. And of course, they're based primarily on signs or symptoms, which, as I have mentioned, can overlap considerably. The diagnostic studies that are performed -- and this is certainly still true -- typically emphasize tissue damage, which as

Page 42

we all know, at least in the chronic pain space, has limited relationship with the actual pain that people report. And then, pain diagnoses typically provide limited information regarding the mechanisms underlying the pain experience.

Ideally, we were going to try to address as many of these shortcomings as we could, given the evidence that's available to us at the present time. And as has been mentioned, a major point of discussion, and probably what we spent more time and more angst over than anything, is should AAPT be evolutionary or revolutionary? This boiled down to can we make a completely mechanism-based classification system?

I think even people who would have loved a mechanism-based classification system recognize that the answer to that question is no. We don't know enough about mechanisms, yet. And if you think about mechanisms, there are different kind of constructs that are important here.

So there's etiology, right? That's not mechanisms. So if you think about diabetic

Page 43

peripheral neuropathy, the etiology is that someone's got diabetes, and that's producing nerve damage, let's say.

Then you could think about general mechanisms. Well, they've got peripheral nerve damage, they may have altered central pain processing. That's sort of a description, not an actual mechanism. Then to get to a specific mechanism, you might propose that there's some dysregulation of TRP channels or something else that is driving the pain. And as you can see, we start struggling when we get far over to the right of what the actual mechanisms are because, again, we don't have the evidence yet.

Another point of discussion is how do we categorize these conditions? Should we categorize them based on location in the body so that all lower extremity conditions go together? And those get to be separate from upper extremity conditions. And well, maybe that sounds interesting, except that that would mean diabetic peripheral neuropathy of the lower extremity and diabetic peripheral

Page 44

neuropathy of the upper extremity are completely different categories even though they share the same process.

So what we decided on was sort of a hybrid approach of system, essentially organ system, bodily system, with some consideration of location, anatomical location. So we have peripheral and central neuropathic pain, which are disorders of the peripheral and central nervous system. We have a variety of musculoskeletal conditions here.

According to site, we have things that happen above the neck. And you'll note that the AAPT system has stayed away from developing classification for headache because that's already been done quite extensively by the international headache group, but we are addressing TMD and other orofacial pains, and we have visceral pelvic and urogenital pain; and then disease associated pains that don't get covered anywhere else. And our two groups here are cancer pain and pain associated with sickle cell disease.

So that's the compromise we settled on, and

Page 45

I think it works fairly well. You might quibble with it, but after a lot of discussion, this is where we ended up.

As you know, we published a Focus article. I should give you a disclaimer here. I'm not the first author because I have any expertise or particular knowledge here. I'm the first author because Bob and Dennis cornered me, and I panicked and said yes.

(Laughter.)

But it's actually a great process to go through, and it was very interesting and enjoyable actually to write the article.

Some of the important characteristics that I think AAPT exhibits and strives for, number one, we want the criteria that get developed -- they're not out yet but working groups are working on them -- we want them to be evidence-based.

We wanted a framework that could be systematically applied across pain conditions so that all chronic pain conditions classified under the AAPT framework follow the same system, which is

Page 46

new to the pain world.

We wanted them to be multidimensional and biopsychosocial. We want these criteria to be applicable for both research and clinical use, recognizing that the uptake initially may be greater for research use, but we certainly want them to be incorporated into clinical applicability. And very importantly, we want these criteria to be living. We want them to update and evolve based on new evidence.

As you've already seen, and as is in the article, these are the dimensions we developed, certainly, the core diagnostic criteria, you really have to specify these, then we can talk about common features. These are characteristics of the condition that are frequent, if not typical, but aren't required to meet criteria for that condition.

There are common medical comorbidities that we thought it would be helpful to specify. And then these two, I can tell you reviewer feedback and a lot of discussion at the meeting focused on

Page 47

these two categories. With a patient sitting in the office today, how do we know that the neurobiological and psychosocial and functional characteristics that they display today, how do we know whether those are consequences or causes of their pain? And the frank answer is we don't, right.

But we thought it was important to acknowledge that both occur. And there is good evidence in the literature that depression, for example, has been found to be both a risk factor that increases likelihood of development of future chronic pain, as well as a consequence of chronic pain.

We thought it was particularly important to acknowledge that there are a variety of neurobiological and psychosocial mechanisms that are indeed risk factors, that are causal in the development of these pain conditions, and in fact there are protective factors that prevent people from developing these conditions.

We wanted this specifically to be

Page 48

incorporated because that's an incredibly important aspect of the evolution of the system. As we learn more about mechanisms driving chronic pain, this gives us a place to specify those mechanisms.

So this is the framework that we came up with from which the working groups are developing their criteria.

Now, these are the nine working groups numbered here. So we have one group working on peripheral and one group working in central neuropathic pain. Then we have three groups working on conditions of the musculoskeletal system. We have a group working on temporomandibular disorders, a group working on visceral pelvic and urogenital pain, and then two groups working on disease associated pain.

So that's what's going on right now, and we have seen some draft criteria come through, so the working groups are indeed making progress, albeit at different rates.

It's also important to point out that right now we're in the AAPT-1 phase. So AAPT-1 is

Page 49

diagnostic criteria based on available evidence, and that comes from literature reviews, existing criteria for those conditions, secondary data analyses and expert consensus. So those are the first criteria that will be published.

Then we fully plan for there to be an AAPT-2, where after these working groups publish their diagnostic criteria, they do studies of the reliability and validity of those criteria and refine those criteria based on new research that is conducted.

At one point in time, we had imagined this would all occur before publication of any of the criteria, and we realized we might all be retired before that would happen. And indeed, we could imagine that after the AAPT-1 criteria come out, independent groups might decide to do research on these criteria and help inform the evolution of the system.

In terms of future activities, we hope that in the next year the diagnostic criteria from all of the working groups will be submitted and

Page 50

published in peer-reviewed journal articles. And then we intend next year to have a launch meeting to talk about the research activities that need to be conducted to get to AAPT-2.

Then, we'd also like -- while these will be published at different times in different articles, we would like to bring them together into one volume so that if somebody wants to have this on their shelf, or on their computer if it's electronic, they can have a combined volume of all the criteria.

So I think the task today is to think about what can we take from the chronic pain taxonomy and apply that to an acute pain taxonomy, and I think we'd do well to strive for all of these characteristics. I doubt we will get much argument from this group about the importance of these.

But I think it's a very open question how these different components of the framework for chronic pain translate into a framework for acute pain. That's going to be the result of our discussions here that will be informed by a number

Page 51

of excellent presentations, and I know Dan will be talking about distinctions among the various stages of pain. But to a large degree, this is our task here. And that's all I have.

(Applause.)

Questions and Comments

DR. FILLINGIM: Yes, thank you.

DR. TURK: We have a few minutes for questions and comments. And just one other thing I wanted to note is, if you look at that list of the nine working groups, that is not an exhaustive list of every possible chronic pain diagnosis.

What we wanted to do was pick exemplars, and hopefully that the template or the framework that Roger described would be used for all kinds of other conditions that other groups could look at. But there was no way we assumed that we could handle every one of the possible diagnoses for chronic pain, but those were exemplars picked because either they were highly prevalent or particularly interesting cases for demonstration.

The last thing I'll say before the other

Page 52

questions is that the supplement that you've heard about will be published in the Journal of Pain. And it will be open access, so it will be available for anyone who wants to get access to it. We're also thinking about -- is this definite, Bob -- mailing out copies of it to IASP and APS members.

DR. DWORKIN: No, we've requested that the publisher figure out how to send copies on a free basis to all the members of IASP in addition to all the members of APS, and that should happen. We can't think of any reason why they can't figure out how to do that.

DR. TURK: Questions for Roger?

DR. RAJA: So in the broad categories that you had, for example, I can think of cancer pain having some neuropathic issues, some musculoskeletal. I mean, there are multiple categories that may be involved in a certain diagnosis. How do you resolve that issue?

DR. FILLINGIM: Yes, and we did have considerable discussion about that, and that's why

Page 53

that kind of category is disease associated pains not classified elsewhere. So if it's a clearly neuropathic pain, we expect it very well will be covered within one of the neuropathic pain working groups.

If it's a disease associated pain that's not covered anywhere else, that's where we expect those disease associated pains will be classified in that group. And, you know, there may be some overlap. There may be the cancer pain working group describes neuropathic cancer pain and refers back to peripheral neuropathic pain criteria or something like that.

Yes, Bob?

DR. DWORKIN: So, Raj, actually what's evolved in a couple of situations for exactly the reason you're intimating, is a bit of a kind of negotiation between different working groups. So in fact, it's ended up that chemotherapy induced peripheral neuropathy, the criteria for that are being included within the cancer pain working group because the cancer pain specialists really wanted

Page 54

to do CIPN.

But of course, the other polyneuropathies are being done by the peripheral neuropathic pain working group, and so we've had to make sure that there's coordination between what's being done by the cancer working group for CIPN and what's being done by the peripheral neuropathic pain group for diabetic, HIV, idiopathic, small fiber sensory neuropathy, et cetera, criteria, and I think we've successfully done that.

The other example of this is lumbosacral and in cervical radiculopathy, which could either be obviously in the peripheral neuropathic pain group or the spine pain group. And it's those neuropathic low back pain and upper back pain conditions are going to be done by spine pain, and they could just have easily have been done by the neuropathic pain working group.

So there are examples where there had to be negotiation about which working group does what. And we just have to make sure, as Roger said, that we can cross reference that. It's kind of

Page 55

unavoidable in a way.

DR. RAJA: Yes, I'm just looking at an example of a patient I saw two days ago. The patient admitted with a history of sickle cell disease, quote/unquote "in acute crisis with basically bone pains." So do you call that patient as musculoskeletal pain or do you call that as other sickle cell pain?

MALE SPEAKER: Yes. Just in response to that, just mention that what you're going to discover very quickly is conditions are what they say they are. So the way we end up defining sickle cell pain would either include or exclude those people by the way that it's been worded in there.

DR. FILLINGIM: Chad?

DR. BRUMMETT: I want to get a sense of what wasn't on the page without turning it into a gossip column. If you look at something like fibro being categorized as musculoskeletal and you call post-stroke pain central, you've got vulvodynia as now genitourinary, right. So we're compartmentalizing again.

Page 56

I know what you think. Like we've talked, and you've got a nice slide showing all these overlap. Is this the right direction? I mean, are we servicing the pain community by continuing to call FM a musculoskeletal condition given that we know so much about what drives pain in fibromyalgia, vulvodynia?

We've got a lot of data out there. It seems surprising in 2016 that we're going to put something out there like this that seems like a step backwards. I'm curious how those conversations evolve because you do describe it in terms of how you made those decisions. But without making this gossipy, help me understand how you get to that point.

DR. FILLINGIM: So I guess one reality is that a patient with vulvodynia has different symptoms and a different presentation than a patient with fibromyalgia. They can tell each other apart, and we can tell them apart. So they're not identical conditions. They may share pathophysiological mechanisms, although I still

Page 57

don't think we know enough about those mechanisms.
We can say the central nervous system is involved. Well okay, the central nervous system is a big thing. How does that help me guide treatment? I can't do a brain transplant. What components of the central nervous system are involved? And why do some people only have symptoms or primarily have symptoms in their bladder or genital organs, and other people seem to have symptoms that they believe and that sound like are musculoskeletal in nature?
At some point, we may figure that out. And that's sort of why we sort of stuck with an evolutionary rather than revolutionary approach.
So what you're asking about is why didn't we go revolutionary. And one issue is I don't think we know enough about specific mechanisms yet, and another issue is that I don't think the research and clinical world is ready for that yet.
But one thing we did talk about is, as working groups specify putative neurobiological and psychosocial mechanisms, it would be ideal, for

Page 58

example in an electronic system, if we could type in, give me all the conditions that involve altered central processing of pain, or disturbances of noradrenergic functioning, and it might come up with different ones. And it sort of starts educating us and pointing us towards shared mechanisms that might underlie these different conditions.
But what you're asking is the very tension that we dealt with. I think we erred on the side of practicality and interpretation of the state of the evidence at this point in time. And, you know, I think there are still plenty of people who would respectfully disagree with that decision.
DR. BRUMMETT: Thank you.
DR. FILLINGIM: Sam?
DR. MCLEAN: Roger, one thing that's interesting to me is -- I think it's phenomenal that you've done this amazing work. The dimensions make sense. It all makes sense, but the dimensions of core diagnostic criteria, common features, comorbidities, et cetera, it's interesting

Page 59

that -- and I say this because it potentially has relevance for acute pain, is that in terms of this taxonomy of chronic pain, it seems like we need to have diagnostic criteria for these pain disorders using these dimensions.
We need to come up with something structured for all the reasons that Roger so eloquently said in his -- that you've said. But why do we need to subdivide them as peripheral nervous system, central nervous system, musculoskeletal?
I get Chad's concern about, oh, is this going to mean that people in the peripheral camp are going to see this as a vouching of fibromyalgia as a peripheral disorder rather than a central disorder, where it seems like it's an argument -- you could argue that you don't even need to make -- you don't need to -- what if you just said, this is our diagnostic criteria for fibromyalgia?
We're not categorizing it as musculoskeletal versus under central. This is like we are developing these categories. You seem to get all

Page 60

the benefits of the categorization without having to worry about someone saying, well, wait a minute, you put it under musculoskeletal. I see it as central because, you know, it's obvious these things are mixed.
So for the acute pain, we could think about at least doing these domains and coming up with criteria, but not saying, and we're going to fit this acute sickle pain under musculoskeletal or under -- because it's an argument that it doesn't matter, it's not relevant for our purposes, and it's just going to create contention or be misunderstood.
DR. FILLINGIM: No, I think that's a fair point. Again, I think part of it was practical, how do we develop working groups and what are the working groups going to be? Is there going to be a central pain working group? Oh boy, well what belongs in central pain and what doesn't? And as far as I can tell, the central nervous system is involved in every pain condition. So that makes it difficult.

Page 61

So at some level, we deferred to existing structures and also the putative locations of the pain complaint.

DR. MCLEAN: I can see how that would have arisen out of the functional desire to have some overarching group above the individual diagnostic groups, and so kind of coming out of that. And again, just with that tension of there could be a functionality of doing that, but maybe the ultimate diagnostic criteria we don't want to put under those sorts of sub-categories, again, simply for the reasons that show a need to and --

DR. FILLINGIM: Yes. Bob?

DR. DWORKIN: There's another very simple minded answer to this question, and I acknowledge that it's very simpleminded, which is we adhere to the IASP definition of neuropathic pain, which is that it's cause by, as you know, all know, lesion or disease in the somatosensory nervous system. And that's how we defined the conditions in the peripheral neuropathic pain bucket and the central neuropathic pain bucket. They're all completely

Page 62

consistent with possibly one exception, with the IASP definition.

DR. MCLEAN: But a disease might obviously involve multiple mechanisms and be much dirty, so that we say, well, wait a minute -- someone says that's musculoskeletal, and it's bone pain, and it's tissue ischemia induced.

DR. DWORKIN: I think at the time our feeling was that fibromyalgia was explicitly excluded by the IASP definition of neuropathic pain from being a neuropathic pain condition. So in a very simple way, that made the decision easy for us.

DR. FILLINGIM: Yes, Kris?

DR. SCHREIBER: So I also think this is a great step forward, and it seems like a good framework for us. I was just wondering, in terms of getting towards precision medicine and taking into account individual differences between patients that may be really, really important in how we go about treating them -- like I'm thinking about someone going into surgery, like they may be

Page 63

high risk/low risk -- it seems like maybe out of your five key dimensions that 4 and 5 were meant to get at that. But I wonder if we can somehow make that of more prominence, be more in the -- work it into the structure of actually categorizing them because I think it may be really important to treatment and how to practically use this.

DR. FILLINGIM: Yes, and that was the thinking there, that a person who meets the core diagnostic criteria for a given pain condition, two different people, both of whom meet those criteria, might have vastly different psychosocial and neurobiological mechanisms driving their pain, as well as consequences to their pain, which can greatly impact decisions about pain treatment.

So I think as we move toward this acute pain taxonomy, it's important to think about how best to allow individualization and personalization of diagnosis and description of pain conditions while creating criteria that can be broadly applied. That's another tension that's important to deal with in this process.

Page 64

Yes, Brett?

DR. STACEY: One of the things that I am always intrigued by is the focus on the underlying pathophysiology, like for instance with the neuropathic pain definition, because a lesion to the sensory part of the nervous system is not sufficient to cause pain. Most people with diabetic peripheral neuropathy, the majority of them don't have pain.

So we get very excited about the things we can test with our available diagnostic criteria, yet, if we're a clinician seeing someone with a pain problem in front of us, the imaging, the lab results, do not distinguish those with pain versus those without.

So I'm very nervous about this pathophysiology stuff thinking that that's part of the diagnostic criteria because I think it's an abstraction. We know a lot about people's structures. You know spinal imaging doesn't really help us much with telling us why this person has pain and why we label this patient as having facet

Page 65

arthropathy, or foraminal stenosis, or whatever it is. But we can see things, but then we make this association, and that association is a big leap of faith.

DR. FILLINGIM: Yes, I don't disagree.

Yes, Steve?

STEVE: Aren't we potentially looking at clumps of forest and trying to come up with labels for the clumps of forest when, when it comes to acute pain, what we really need to define are the trees in that clump of forest?

So if you have someone who has a burn injury, and that is their primary acute pain diagnosis that should allow you to develop treatment plans and to prognosticate, but they may also have really, really significant biologically based anxiety that completely messes up how they personally deal with their pain, it seems to me that that's a different diagnosis.

Our job isn't to treat and prognosticate about that anxiety diagnosis. Our job in this meeting is to come up with the taxonomy to actually

Page 66

define those other categories. And that's a different way of looking at it because, I mean, we all understand the comorbidities and how they interact and nothing is simple, but if you really are looking at defining a taxonomy, it has to be simple. It can't be complex.

I've been struggling for months dealing with the cockamamie structure you guys came up with --

(Laughter.)

STEVE: -- because it's really hard for me to take that and do anything clinical with it.

DR. FILLINGIM: In fact, we thought about calling it the cockamamie AAPT.

(Laughter.)

DR. FILLINGIM: But there was some -- no, but I think this is a good point, Steve, because what we're talking about is -- the core diagnostic criteria for burn pain can be defined, I assume -- I don't know anything about burn pain but you guys do -- but then, on these other dimensions, which are not required for that diagnosis, some patients may have strong psychosocial drivers of

Page 67

their pain phenotype and other patients may not. And that's why there's this sort of multidimensional approach to the framework.

So you all can decide how this applies to acute pain and which parts of a multidimensional framework are important. But you're right, there has to be something that's a core criteria for the pain condition itself because the anxiety is not the pain. It's something that accompanies the pain either as a driver, or a consequence, or both in some patients.

DR. SCHUMACHER: Mark Schumacher, UCSF. To expand on the difficulty rather than clarifying, what is the target audience for the products? So I'm facing two issues, as many are here. One is UCSF, as well as other institutions, are centers of excellence in pain education, and there's a national effort. So we're looking at ways to simplify approaches of learning at the undergraduate across all professional schools.

Then in addition, as you know, many of us are launching efforts to develop ACGME sponsored

Page 68

regional and acute pain fellowships. And these are the two targets that we are wrestling with, and I would hope that the products that would come from this -- I know I'm a newbie here -- but the product would at least gesture to those audiences. I think it's going to be very important in the long run. Thank you.

DR. FILLINGIM: Patrick and then Henrik.

DR. TIGHE: Roger, my understanding of this approach is that we have several dimensions, and then there are the exemplar pain objects that are described by the dimensions to create the diagnostic pattern. So that ends up being, at least from my understanding, a relatively flat structure.

Is there any intention to add some vertical depth of clustering this, similar to the DSM structure where you have a hierarchal representation of types, and subtypes, and sub-subtypes organized under some type of structure, or was this intended to be flat with specific diagnoses running in parallel to the

Page 69

attributes at hand, specified by the dimensions?
DR. FILLINGIM: I can't answer that because I'm not sure I understand the question. So what would be -- give me an example of the DSM vertical piece you're talking about.
DR. TIGHE: So we might start with mood disorders, and then we'd separate under anxiety versus depression, and then within depression, you would have certain subtypes. Is there a plan to move along something for the chronic pain, or is it meant to be separate free to those nine exemplars?
DR. FILLINGIM: I'm not sure we talked about things at that level, and maybe that's this categorization that some people have already mildly objected to, which is there's musculoskeletal pain, and within that there's different types of musculoskeletal pain or neuropathic pain or whatever.
I don't know that that's sort of an exact parallel, but that's probably the closest that we come at this point. But, you know, if we get smart enough, that might change, and there might be a

Page 70

different vertical structure. And maybe we'll satisfy Chad, and there will be centralized pain or something like that, and there will be different conditions that come under that.
Bob or Dennis?
DR. DWORKIN: I don't know if this is what you're thinking of, Patrick. We sort of have a hierarchy. I don't know that we've thought about it explicitly, but it's not an exciting one. It would be something like neuropathic pain, peripheral neuropathic pain, polyneuropathies, diabetic, idiopathic, CPIN, HIV.
So that's a kind of hierarchy. I don't know that we've emphasized it, but it exists. It certainly exists in the way that we're structuring it.
MALE SPEAKER: [Inaudible - off mic]. Actually, it just doesn't seem like -- it seems like the fundamental goal here is that when someone says low back pain, that we're using the same criteria, which is such a huge thing because there's nothing [inaudible – off mic]. That is a

Page 71

massive benefit. To try to characterize these things in ways, which, really, they're very dirty -- let's take PTSD under anxiety disorders.
PTSD has overwhelming comorbid depression with it. Depressive symptoms are a huge part of PTSD. We don't need to go into these vertical silos that are inherently going to be wrong and they're going to be -- when you talk about bone -- okay let's say sickle cell, you would mark that area with the peripheral nerve in it. You've got a neuropathic component. Someone seeing these patients.
What utility is there for making vertical structure that's going to inherently be wrong or incorrect when we're simply trying to come up with diagnostic criteria that can be used uniformly around the world?
DR. FILLINGIM: Steve, I think you had a comment on this.
STEVE: Yes. Those are great questions. I think one thing that -- and this is going to be several years before we can ever do this. But I

Page 72

think were we to put together a AAAPT taxonomy successfully, based on whatever we come up with here today, keep in mind we can always go after the fact, assuming we're collecting data, and answer those questions about taxonomy empirically, because in all likelihood, we are wrong about how we would lump things together and the assumptions we would make.
But I think one thing we've learned that is really important from the initial AAPT for chronic pain is that we have to start somewhere. And we may come up -- well I'm not going to say may. We will come up with something that is imperfect. And if we have a starting point -- and you'll see in my talk tomorrow why it's beneficial to have some starting point. That gives us something to work with to try to improve that and opens up the possibility of empirically looking at other things.
I just wanted to make a comment that we had a couple of questions about the multiple dimensions. The Dimension 1 is the core diagnostic criteria. It would be useful in education settings

Page 73

because it is really like a cookbook.
It's like if you want to know what this condition looks like, read Dimension 1, and this will tell the core features, to somebody who doesn't know that condition, what it would look like in clinical practice and how you would go about assessing.
The Dimensions 2 through 5 are messier, and I get the feeling that some people are a little bit uncomfortable with that. In the original AAPT, it was recognized that not every condition has the same comorbidities, not every condition has the same factors that are impacting on it or consequences of it.
So it had to be kind of different for everybody, and we didn't -- and I'm kind of realizing as we're talking about this, we never really got down to saying how you would systematically assess all 5 dimensions for a given patient. So it's kind of left up to you to decide how to assess 2 through 5.
I don't know if it's doable to do more than

Page 74

that or not, but I think that's something that could be discussed today, or would you want to include, for example, anxiety assessment officially in every disorder on a particular axis.
DR. FILLINGIM: Dennis?
DR. TURK: Although we didn't discuss the assessment of those in Roger's paper, in the supplement, at least the chapter that I did and the one that Rob Edwards did, are focused in on how do you go about assessing these things.
So if you believe that emotional factors are relevant across conditions, what are the ways that you could go about assessing that in an efficient way? So we did try to go into that without recommending specific measures but just giving, laying out, here are the ones that have been most commonly used.
You know, a tension that I've heard, and I think Steve is picking up on this, and one that I think John Loeser -- this goes way back to when we first talked about this, is although those of us who did that manuscript all believe that all five

Page 75

of those dimensions are important to consider, that many people will look at 1 and stop.
This is what's happened in the old DSM-4 is that people rarely use these subparts. It's what happened in the old IASP classification, people stuck with the first one. And unfortunately, if you're going to put a priority, if you're going to list these in any way, if you have to list the core at first, everything else then becomes secondary.
That was a tension we had at the meeting and I'm picking up from the comments here, is how do you balance the fact that for every individual is an individual. And regardless of what the nature of the pathology may be, all of these other factors have influence, and how are you going to see them.
So the question will there ever be subgroups, empirically we may identify that within one classification there are subtypes of people. Not everybody with painful diabetic neuropathy also has this set of other characteristics. So we may get there, but we're not there by any means.
Roger put up AAPT-1 and AAPT-2. Well, we

Page 76

have 3, 4, 5. As the data comes along, what we had hoped was the structure would be useful to help us advance, and it will be modified as we go. But at least people attend to those important dimensions as they're thinking about their patients as a group, and then the individual patient by patient.
When you get to that level, then you're going to have to make some decisions as a clinician, which may or may not exactly follow everything that's in the classification. But at least we would like you to think about more than just Dimension 1.
DR. FILLINGIM: Steve?
STEVE: [Indiscernible – audio distorted].
MALE SPEAKER: Speak louder.
STEVE: Okay. My colleagues -- or if a doctor's doing musculoskeletal medicine this afternoon, are going to do probably seven or eight ultrasounds for tendinopathy on patients, if they even think about looking at catastrophizing and some other things, even though these patients are sent for acute pain, if the dimensions work the

Page 77

right way, just for them to screen for some of these things is going to be a benefit.

So if we look at our acute pain guys or sports medicine guys, they rarely look at that until 3 months or 6 months, or until they refer them to a pain doctor.

So within the dimensions -- hopefully, this is actually going to be helpful. I think we're maybe jumping way ahead. But some of these basic ideas, even though it's very common to us to think about psychosocial variables and all that on the chronic pain side, the acute pain clinicians rarely think about it.

So those dimensions could actually work even if they're starting to use a screening tool. So maybe that would be in the 4th and 5th dimension to look at those things.

I'm just kind of throwing that out there. I think we always think of pain clinicians versus the guys doing acute pain, where it is based on mechanisms. But we could give them more options to kind of work in a hierarchal way. That's all.

Page 78

DR. FILLINGIM: And I could see that being a huge benefit if this kind of invigorates acute pain care and diagnosis with the biopsychosocial model much more than it's invigorated now.

Dan?

DR. CARR: So I'd like to, for the sake of advancing the conversation, try to make explicit what I think is implicit in many of the comments, mainly that while the classification is fine, it comes from a tradition of looking at mechanisms in a sense that are cellular, or the more micro scale the more secure one feels about a mechanism or its value, and progressively assigning less and less value to the more macro scale things, such as these social interactions or the presence of risk factors, but we know that those are very, very important.

Actually, I was delighted to see, in the slides that Knox will show, a reference to Roselyne Rey, who wrote on the history of pain, to say that with the successes of the scientific method, medicine's concept of illness shifted from

Page 79

something that befell an individual with that individual's complex life and social interactions, to something was a physiological process that was just hosted by the host who happened to be the host of the process.

So where I'm going with this is to wonder if there might not be another access or another dimension, certainly for chronic pain, but I think also for acute pain, that captures the social interactions or meaning of the pain or of the illness.

We're often inclined to focus on these micro scale mechanisms, and I'll get into that in my own talk, yet we go out and practice in the real world, and all these distracting irrelevant things, like the meaning of the illness, the economics, the patient's family, these are kind of brushed aside because we think we're focusing on the real mechanism.

Not that this classification is wrong, but it's the things that we're trained to brush aside which may be major determinants of outcomes in the

Page 80

acute pain setting as well as the chronic pain setting.

So I guess I'm calling for another axis or something to be added that renders explicit the implicit feeling of clinicians that when you get down to an individual level, there are a lot of these factors that we're trained to brush aside that actually are really, really important.

DR. TURK: That's in Dimension 4. We'll look carefully at Dimension 4, and when you see the supplement paper, many of the things you just mentioned get embedded in there.

So it's this tension that we keep talking about, which is what's priority and important makes the secondary uninteresting. We were trying -- and we never resolved it well, how to make sure that it's not one's more important than the other, that all of these should be considered as you're evaluating your patient.

However, if you don't start with the presenting symptoms and signs, you're going to not be able to even start with somebody. But that

Page 81

doesn't mean you don't do all these other things. It only means that these then are relevant.

I keep using the word we'd like you to consider, so I don't care if you're in acute care, I don't care if you're primary care, or chronic care, these factors should be things in your mind when you see that patient; not they're secondary, they're uninteresting, they are small, once I know the pathology I'm done, because every one of the clinicians in here knows that knowing the pathology, you're not done with that patient. You can have very different responses from people.

Henrik has had his hand up for a while, and we're going to get to him.

DR. KEHLET: It was the same question.

DR. FILLINGIM: Bernie?

DR. SCHACHTEL: No, I agree. I mean, we're really talking about a patient-centered approach towards acute diagnosis, treatment, and prognosis. And I think that all this can be simplified in some ways by taking the first grouping, the signs and symptoms that you were just talking about, Dennis,

Page 82

and combining it with a third axis, if I can use your terminology, because what's important to the patient may be really what matters.

I refer to the phrase, I think it was in your third ranking there, third categorization for chronic pain, you used the word "descriptors" of pain. And often the patient will describe his or her pain not in conventional, shall we say evaluative terms, but more qualitative, and often emotional or effective terms, where on the case of acute pain, especially in sensory terms. And that's what matters to the patient.

So I think perhaps we could consider a more -- I don't know want to use, and perhaps I shouldn't use the term "holistic." But originally I had described this in earlier papers as patient directed endpoints. And now the terminology, which is more accepted, is patient centered endpoints.

Maybe what you're getting at, Dennis, if I understand you correctly, is we really have to look at all of those dimensions beyond the very first to get to what really matters to the patient. It gets

Page 83

to the question that I think Steven was asking before about how do we treat the patient.

Well, in many cases, that patient comes to you with, let's call it post-operative pain, but the catastrophizing, the magnification from the past, may seriously implement -- rather, affect his or her perception of pain and how he or she responds when you even ask for a grading of pain.

DR. TURK: We tried to capture that, and probably it slipped by in the phrase biopsychosocial, that is all of these should consider all of those factors in the individual patient and in the classification.

So that was our attempt, but I know John Loeser and I, Bob, went round and round about the dilemma of not letting it turn out that you only pay attention to what historically has been just the physical pathology.

But you've heard it enough times here. It's still a problem by calling one core, and then these other comorbidities, characteristics, potential causes and consequences. It's not those are

Page 84

secondary, it's just that they need to be there. But we ran into the dilemma -- Roger remembers this well -- is how do you deal with what's going to be where you start, and that's the dilemma we ran into.

MALE SPEAKER: Roger, could I just respond one second?

DR. FILLINGIM: Yes.

MALE SPEAKER: Perhaps it's the way we present it, not as a list as opposed to a Venn diagram, that there are interceptions of all of these dimensions. And maybe that way, the reader, the educator, the clinician will also see them as interrelating as opposed to sequential or, as you said, primary and secondary.

DR. FILLINGIM: Yes?

MALE SPEAKER: So I just wanted to second what Mark Schumacher had said. One of the important things is the ASGME's under consideration for the acute pain fellowship. I think here's an opportunity for this group to influence how teaching is carried out across the United States.

Page 85

And not only that, but convert these individuals from being just block jocks to actually creating an acute pain paradigm that people can follow through.

So here's an opportunity, but just to follow up, I think there is a real need to move this agenda rather rapidly than to sit around because in the event the ACGME does approve this, there is a likelihood that this could even be up and about for '17. So we have to keep that in mind.

DR. FILLINGIM: Okay, thanks. Yes, Paul?

DR. DESJARDINS: Roger and Bob, just a question directed to both of you to bring in a different dimension of the discussion. There are, at least at last count, 200 companies developing therapeutic agents, devices, techniques, who are looking at various acute pain conditions.

They come to it with a very simplistic question, where do I start? Do you have a model? Can you show me one study where I could get a basis for making a decision the concept works for this group of categories? And this has been a discussion that has gone on at least for 35 years

Page 86

in my discussions with FDA colleagues, and they're common questions.

So with that as a preface to the question, to what extent have the chronic pain positions, this position paper on categorization, how much does that influence the discussion about the developing drugs or devices for chronic pain? Has it crossed over to that? And does that provide a model for sort of how we might have a better roadmap going forward?

DR. CARR: So Paul, that's a great question, and I have to disclose that from the outset, the way I thought about the chronic pain effort is that it's potentially inclusion and exclusion criteria for clinical trials. And that if we succeeded at our job and developed valid, reliable, clinically useful criteria, that these will be what's used in clinical trials.

It's up to this group to decide whether to think about the acute pain diagnostic criteria the same way, but I think most if not all of us in the chronic pain effort started off thinking of these

Page 87

as inclusion/exclusion criteria. They would of course be helpful in education, in the clinic, et cetera.

DR. FILLINGIM: And if I could just add to that. If I go back to Patrick's question about sort of vertical structures, is there a group of pain conditions for which compound X is helpful? And what falls under that group? And what's the prototypical or accessible model for that group of conditions?

That would have been lovely to do with chronic pain. I don't think we're actually there yet. It might be more feasible for acute pain, but that will unfold as the discussion.

MALE SPEAKER: I'd make a response to that also. Just to add, when you brought that up, I heard -- and not to put John on the spot, but you said how much impact does it have. John says "Absolutely none at all."

(Laughter.)

MALE SPEAKER: Now, here's the point I want to make though, is that I'll talk tomorrow a little

Page 88

bit about our experience with complex regional pain syndrome diagnostic criteria. And I can tell you that once those were published, what happened was about 10 years, they started being adopted internationally, once they were published in Pain, started being adopted internationally. And now if you look on the clinical trials website, you see everybody is using them, and it has become the norm to use this.

So even though you are rightfully skeptical, I think it is possible if people are dissatisfied with what exists now, I think there is a very good chance that these will be adopted if they're well thought out.

DR. FILLINGIM: Sean?

DR. MACKEY: I want to add my compliments to what you and the group did. And just thinking ahead from an operational standpoint, ultimately, you want to use this classification system not only for pure research purposes, but ideally you'd like to get it in the hands of clinicians to be able to classify and characterize large numbers of

Page 89

patients.
As I'm thinking as a clinician and thinking of the folks in the trenches, they're already inundated with these other classification systems. So the question is, was there consideration, and should there be consideration here, towards tying in more closely with an existing classification system, like ICD-10 or SNOMED, that's been around for decades; identifying the features of it that are working, and then build on those features and add in the things that we would want to have it expressed in either chronic pain or acute pain. But not ask the clinicians to learn yet another classification system when they're already struggling with ICD-10 as it is and there's these other systems that are already in place.
DR. FILLINGIM: I can say by my recall, we didn't really consider sort of ICD-9 or 10 and trying to match with that. Whether that was an error, I don't know. And maybe that's something for the group to discuss here on whether that's important for acute pain. But I think you hit on

Page 90

another tension, which is it's got to be clinically useful and not such a burden over and about what clinicians are already asked to do.
DR. MACKEY: Right now, clinicians are terrible with diagnosis. We build into our EMR data, and the quality of the data is just absolutely terrible. We're hoping ICD-10 will help, but we have to teach clinicians how to diagnose and how to code it properly and integrate it into their workflow, which they're not doing now.
I love this classification system. No concerns about it. Other than the operational nature of it, we're trying to get this into the real world to collect huge amounts of data.
DR. FILLINGIM: Yes, that's a good point.
Patrick, maybe this will be the last question before the break. Are we on schedule for a break now? Yes, Patrick?
DR. TIGHE: For the third dimension, has there been discussion to create an exhaustive list of terms to capture the range of possible values

Page 91

for that dimension? So is there a range of common features that you can choose from to describe something?
If that list were comprehensive but also complete, meaning finite, you had to choose from something there and you had stage upgrades, then you'd have a structured way of rolling this up and categorizing different types of pain. I didn't know what the vision was for how you intended to characterize each of those dimensions.
DR. FILLINGIM: Yes, I can say I don't -- at least I haven't thought about a comprehensive list like that. But the supplement that's coming out takes a more conceptual approach and gives examples, not a comprehensive list but examples of ways to assess different dimensions of the taxonomy, but not sort of comprehensive in the way you're suggesting that might be useful in an EMR type of sense and for text analytics and that kind of thing.
Did you have a quick question, Deb?
MS. GORDON: Well, I'm sitting here as a new

Page 92

person to this, but also as a clinician thinking that the diagnostic criteria for acute pain seems to be less of an issue. When someone's in front of you and they've had a big incision or they've had a big burn -- so I'm thinking of it very differently in terms of do we have to look at tissue type, the visceral pain versus myofascial pain, or is ischemia different from in cellulitis or infection? It just seems like it's kind of a different set of things we're going to be talking about.
DR. FILLINGIM: Yes. So what I hear you saying is, you guys have it easy. We took on a much more difficult task for the chronic pain taxonomy, and we should all be congratulated.
(Laughter.)
(Applause.)
DR. FILLINGIM: So we'll take our break now until what -- are we back at 10:00? Is that right? 10:15. Great.
(Whereupon, at 9:47 a.m., a recess was taken.)
DR. TURK: Welcome back. Obviously there

Page 93

was lots of discussion going on, which means we're succeeding. Roger did a terrific job. The conversation or discussion that we were having after Roger's presentation is exactly what we need to get out there, realizing that Patrick and Michael are going to take all this information, and by the end of tomorrow we're going to have a definitive draft manuscript for you to see.

So we're going to now have our next presentation. The man who is already introduced, Dan Carr, so you already know who he is. And he's going to give us a little bit of a perspective on acute, subacute, and some other concepts that are particularly important.

Dan obviously is the president of the American Academy of Pain Medicine, and he is from Tufts University, and other places.

DR. CARR: And long-term member of IMMPACT.

DR. TURK: That, too.

Presentation – Dan Carr

DR. CARR: So once again, I thank everyone here. It's a phenomenal group. And what I was

Page 94

going to be talking about, the title is Key Distinctions Among Acute, Subacute and Chronic Pain. I'll emphasize them, but I'm going to cover some more ground, so I thought I'd start out with this slide.

I heard about this quote from my friends at Cochrane in Oxford, and they do this all the time. If you have a systematic review or a clinical trial, just because you can discern a difference, is that really important?

I think this would be a nice thought to keep in mind for the conference going forward, that if we come out with some theoretical idea or hypothesis that's very intellectually attractive, but no one uses it, it's not helpful, it doesn't add value, then we probably have failed.

So if we are trying to make a difference, then that will determine whether this has been worthwhile. It's not enough for there just to be a difference, it has to make a difference.

So we're fortunate to have in the room people, certainly I'm thinking of John, who were

Page 95

there at the outset of this definition of pain. It's always struck me. If you look at the definition, there are two things that have struck me.

The first is how I came to realize that every word was fought over. So certainly pain would not be pain unless it were unpleasant, and that gets to the anecdote about Howard Fields' proposal for the term algosity. And we know there had to be actual or at least potential damage, or described in such terms.

In subsequent iterations, the insights were added that language or verbalization were not required. But I'm not 100 percent sure why this particular collection of words was arrived at, but one thing that's always struck me is that this emphasizes the real time.

Now, you can argue that this is certainly applicable to chronic pain or persistent pain, but the wording itself I think did not initially address the important role of plasticity and chronification of pain. And I have some ideas

Page 96

about it.

I personally feel that it was building on the wonderful successes of neurophysiologists, in particular electrophysiologists, of the '30s, '40s, and so on, who were able to map out pathways, study properties of neurons by doing real time stimulus and recording. But that's the definition.

So I'm going to give you what I would call context or constructs to guide this notion of where we need to go as differentiated from where AAPT has been. I'll give you a personal take on this, but I think it represents the thoughts of many people, that if we're thinking about the context in which we are constructing a taxonomy, and we're thinking about chronic pain, issues of making the diagnosis are very important. And you will hear from world authorities later, Steve Bruehl is going to talk about this, the criteria. It's already come up.

When clinicians think about chronic pain, behavioral dimensions are embedded and integral to this, things like suffering, trauma, anxiety. If we see a patient with chronic pain, we presume that

Page 97

their pain is centralized, and hence, they have hyperalgesia, other things. But we're also frustrated because by the time, as a clinician, we see a person with chronic pain, there's no opportunity to prevent or even modify the inciting event.

Also, the intensity of pain, as we all know, is only one of several outcome domains that Bob and Dennis have pioneered in constructing and helping us think about. For the most part, I'd say the patients we see with chronic pain are stable medically. And as I just mentioned, I have had a feeling that the chronicity is something that's underweighted in what I would call a real-time definition.

Finally, just as a practical matter, there's an outpatient culture of care. So what we're thinking about is in John's diagram, which is nociception caused pain, which led to suffering, and which frequently leads to pain behavior.

In contrast, and I've worked on acute pain services as well, the diagnosis is usually less of

Page 98

an issue. Making the diagnosis is less of an issue.

Anatomy is relevant. It may not be relevant from a mechanistic point of view, but in a practical sense, if someone has a lower extremity procedure, it makes sense to do a block, epidural spinal, whereas it may not be relevant in a head and neck operation.

For the most part, the framing of this, and you'll hear a wonderful framing and summary of this from Tim Brennan later, it emphasizes I'd say the periphery and cellular or micro mechanisms. And of course, we have an opportunity not just to intervene early, but even to prevent pain.

Although pain intensity has been criticized, justly, as not capturing the complexity of the pain experience, nonetheless, it's a really good outcome measure. And thinking ahead to the points that Bernie made and Paul made, in terms of getting drugs approved, we have an opportunity to have quite a bit of influence going forward if we can add value to the traditional reliance on pain

Page 99

intensity.

So for example, as we had our discussion after Roger's talk this morning, as we're thinking about things that may be important, this issue of social, families, the connectedness, might in fact turn out to be as strong a determinant of outcome or long-term outcome as whether a person is a placebo reactor.

So we've addressed placebo reaction, but there are a number of other behavioral or social issues connected with expectation that could work in a negative way.

I think as Sean pointed out, we're in an era where people are collecting data. We have normal routine use of electronic data capture, so we have objective outcomes that can be easily captured in terms of big databases, like length of stay, or incidence of complications.

On the other hand, in the acute pain setting, patients are often unstable medically. They may be post-op, they may have fluid shifts, they may be hypotensive, they may have had trauma,

Page 100

whatever, to the thoracic cavity, they may have respiratory issues, organ damage, and so on. Or if they're ill enough to be in the hospital, maybe they have something like pancreatitis or sickle disease where you really have to keep the vital signs supported.

That gets to the last point, which is that a lot of the acute pain assessment and treatment is conducted in an inpatient culture of acute care. And that goes for labor as well where there's a lot of observation, a lot of scrutiny, interventions take place quickly.

So maybe this is a bit of an exaggeration, but to illustrate that mentality of focusing at the micro level, I'm positive that this title of an article, whose senior author was John Levin and it appeared in a supplement after one of the IASP world congresses, I'm positive this was chosen to be a little provocative. But the title that he gave the article was called The Fundamental Unit of Pain is the Cell, so I think that embodies one extreme.

Page 101

So what are we talking about here? I think when we construct acute pain versus chronic, we have something like this ball in a well. If there's a little bit of disruption for a little bit of time, then that ball which started at A rolls up the side a little bit and then it kind of settles back down. But we often think that if the intensity of the pain stimulus or the intensity of the trauma passes some threshold, kind of roll that ball up to point B, and if it's over that threshold, it gets pushed over to the right, and we're in a whole different ball game.

But I'm going to propose to you that maybe we've over simplified. And I think it's fascinating to hear the conversation and discussion from clinicians this morning that we feel that there's more that we could capture, that there are things that are not captured yet, that might be very important for outcome or judging the success of any therapy. These are these social things. I'll get at that in a moment.

So we're developing analgesics, and if you

Page 102

were a group of students, well I often show a slide like this, but before I put the slide on the screen I ask them, what do you think is the everyday common analgesic that has the greatest benefit to risk/ratio?

Of course, the answers are Tylenol, aspirin and so on. But in our daily life as a species, all the time, children get injured, and all the time their mothers, generally their mothers or care providers, nurture and provide reassurance, and it's a great intervention. It works 99 percent of the time. There's no ill effect that I'm aware of.

So what's going on here? Well, this is a picture taken from the stage of a marionette show in Paris. And you can see these kids look to me like they're 6 or 7 years old. They're completely engrossed in this, but what they're watching are traditional marionettes with strings. It's obvious these are not -- they don't look anything like a living person. They're puppets.

You can think about your nieces or nephews or kids or grandkids watching cartoons on TV that

Page 103

they know are cartoons. But they get so wrapped up in it that they're lost in it. And I bet if you took any one of the kids and said, Pierre, you know this is a marionette, right? He would probably say, yes it was, but they just can't help themselves, they get drawn into things.

So this leads to the issue of what's going on. How can they get so drawn into this? And as we know, we are well beyond the classic view of pain where there's some passive registration of nociception, and we don't much think about what's going on. Our current view is that this is a complicated thing. There's a network of brain structures. It takes in nociception, but other inputs and memories, and actively constructs an internal model of reality, and we don't really know how that model works. It's probably really complicated. It is really complicated.

We know from work -- and this is from Sean's lab, that -- and I'm just reminding you of this, everyone in the room knows this -- that empathy for another's pain is as effective in some regions of

Page 104

the brain in activating those regions as is pain in oneself.

Looking at another dimension of this, this classic study by Tor Wager looked at rejection paradigms and found that if you looked at negative affect induced by pain or rejection, that there was a similar overlap in many regions that are activated by both circumstances.

So if we wanted to look back and say, well, the issues of the experiential side of pain are now attracting more attention because we're in a situation where we can speak with people, they can report how they're feeling, and at the same time we can do imaging, this has placed greater weight on the experiential side of pain.

So it's often worthwhile to look back and see, well, who has talked about this. There is an immense literature, as old as all of literature, that refers to pain. The actual origins of this Book of Job probably took place in the 6th century before the common era, even though they were later incorporated into the Bible, this was an older

Page 105

story.
Job had some illness. He had some kind of a rash. He felt bad. And what was the result? The result was that the people around him, even the children, rejected and vilified him. So this language is really strong emotional language. He said, "They abhor me. They flee far from me. They spare not to spit in my face." So very strong language.
There were a couple of articles, I'm happy to give the references to you, written by some Greek anesthesiologists. One was around 2000, one was about 2010. They looked at Greek medical writing in general in the first article and in Hippocrates in the second article, and traced out different terms of relevance to anesthesia and also analgesia and pain.
It's very striking that the Greeks were outstanding in their linguistic ability to relate experiences because they didn't require any technology to do this. They could just observe themselves and others. Some of the writings are

Page 106

just remarkable.
But the point of showing you this is that they differentiated at least three different types of pain. The word "algos" is derived from a root meaning to care or look after. And this tended to be used in the context of somatic pain, and there are many compound forms that link this to pain in a certain area.
On the other hand, the "odyne" was the psychic dimension of pain. And the literal translations of the context in which it's used and the compound forms are things that don't look that different from the McGill Melzack scale. These were just literal translations of what these compound forms meant, fearful or terrible, acute or hot and cold.
Then there was this other term called "poine." Poine is the root for payback, or retribution, or penalty. It is believed to come from an earlier Indo-European route meaning to pay, or atone, or compensate.
Certainly, this is the way it appeared in

Page 107

the Book of Job. There was the immediate assumption that Job displeased God, or had done something wrong. And from the outset, his illness was viewed by his community as payback for something, and much of the Book of Job is spent trying to figure out what he did.
In Latin, this evolved and kept its meaning to mean penalty, like penitentiary for instance. And even in English, it kept the connotation of punishment, and there's some legal language, like something being punishable on pain of death. And in that context, it doesn't mean nociception, it means penalty.
So I would propose to you that, to me, it looks like the word that we've chosen, that we've settled upon, of several different dimensions, is the one that has a social or transactional meaning.
I'm glad that Bernie is here. He'll recognize this table. This is the table from the famous Lou Lasagna article with Beecher on the powerful placebo. And they used the term "reactors" instead of responders as we would, or

Page 108

"non-reactors."
I'm not quite sure how they came up with these categories, but they characterized the individuals whom they observed in terms of whether they had a certain attribute or did not. And it's striking to me that if you look at things that differentiated, the placebo reactors from the ones who are not reactors, this one, you can't quite see this here, but there's a statistical relationship.
If the patient liked everyone in the hospital, or if they thought the care was wonderful, and if you looked at regular churchgoers -- I would come away from this saying that the original construct I showed you a few slides ago, where you have one kind of conceptual compartment and that's acute pain, and that's mechanistic, it's all about what the cell is doing versus the construct we've made of chronic pain is a false dichotomy.
I know this whole talk is in a sense creating a false dichotomy, but I'm trying to emphasize the fact that when you look at the

Page 109

literature, there are already many cues, including Beecher's own observations of people who didn't feel a bullet when they were wounded in battle because it was a way out of battle versus those in everyday life back in his Boston practice who did feel the same injury much stronger.

If you look at this literature on acute pain, there actually is a substantial framing of acute pain, and that relies on memory inputs. We asked our Tufts students last year, we were inspired by CNN because when the Pope visited the U.S., they did a quick word cloud and they said, "Write three words about the Pope." One of them was opposite of Trump.

(Laughter.)

DR. CARR: But others were things like compassionate. It's true. So anyway, we thought, you know what, it's pain month; why don't we do this?

So the question is what three words should the world know about pain? We sent it out to our mass mailing list, students, friends, alumni,

Page 110

faculty. And this is what they came up with. And we didn't cue them at all, this was it. This was the whole thing.

So I would propose to you that to people who either have pain or are close to or treating those with pain, this experiential aspect of suffering and shame is really very important. And nociception or the magnitude of pain itself is just one component of this. There's a couple of words like "discomfort" that fit in. But fundamentally, this was more about the experience of loneliness.

Now, Leo Goudas and I wrote an article some time ago -- so I've been beating this drum for a long time -- it stated in the Lancet article that acute versus chronic is oversimplified. And if we look at work, which was available even back in the '90s on the expression of genes, let's say in dorsal horn, you could see c-Fos expression within tens of minutes of an acute injury.

So what I propose to you is to try to think about acute pain as the initiation phase of persistent pain that is mediated through a cascade,

Page 111

which in most circumstances in acute pain is triggered by tissue injury. And as in many other complex systems, like you think of the butterfly effect, a small change in the initial state of the host or in some aspect of the nociceptor stimulus produces major differences in the detailed manner in which this process unfolds.

So should we be thinking about acute pain as the initial phase of pain the disease? We know that injury triggers a cascade of responses. We know the peripheral and central nervous systems have evolved to promptly adapt and reorganize and remember.

So there's an essentially programmed instability. In other words, it's like a mousetrap. A mousetrap is a contrivance, which works because it's unstable. It's all set to get triggered with a little stimulus of a mouse paw on the cheese. But our nervous system has also that programmed aspect, and it's programmed to achieve instability.

So we know that there is a lot of chronic

Page 112

pain after surgery, and it's a really interesting question, why the number needed to harm isn't one? Why doesn't everybody get chronic pain after everything? There's been a lot written, and I'm certainly going to defer to Tim and others in this room about the chronification of pain. But this is a key new appreciation that's been driving this whole area.

So acute versus chronic pain, maybe that's oversimplifying. Maybe there's a disease state, and you can think of this like infection, or like tumors, where my understanding is that every day we make a number of tumorous cells or cancer cells, but our body mostly cleans them out. And when we shift our ability to do that, let's say getting older, immunosuppressed, that's when they continue to grow. But the process is always potentially going to occur at any time.

So maybe there's a chronic disease state that may begin within hours or even tens of minutes of acute injury. And I would say that the techniques to effectively suppress that cascade and

Page 113

the following benefits have perhaps been inadequately studied. The mechanisms of how the pain normally resolves, through these, for one example, a compound class called resolvents, are an intriguing area of study.

So we're here at this juncture where the people who study pain in the acute setting have focused on the micro scale, kind of a bottoms up. But we know, and it's especially intriguing to hear about big data from Mike and Sean, that maybe we can benefit from thinking about pain as a population-based phenomenon. Maybe we can add something to that.

So I'm proposing to you that maybe this question of when does acute pain, maybe it's misleading. Maybe we've been misled by framing the question that way because we're equating time course and mechanism. But we know that there are many instances of prolonged pain or repetitive nociception that can be resolved, and there's no chronic pain thereafter.

I was intrigued and I referred to this, I

Page 114

was very influenced by a paper that Henrik Kehlet wrote with Fred Perkins probably 15-20 years ago, looking at risk factors for persistent surgical pain. And they used the term "psychosocial factors" as kind of a term because we knew there were some patients, and we know this in the acute pain clinical world, that are not going to do well.

We don't have a convenient way of dealing with that, but I think there's a clue there that it may be very valuable to transpose or take over some of the dimensions that were used in AAPT that traditionally we tend to reserve for chronic pain into the acute pain setting and do more with them.

So we need to distinguish between this concept, and I gave you some samples from the acute pain shared interest group of AAPM, that acute pain is tied up with intense nociception versus the onset of this reorganization process that we call chronic.

So if you look at the literature, and I don't mean to oversimplify this, but in some crude way, it looks like the chronic post-surgical pain

Page 115

risk is somehow proportional to the magnitude of peripheral nervous system injury and the magnitude of sensitization that in turn can be triggered by poor pain control or high pain intensity.

But there's so many factors that modify this: genetics, epigenetics, cognition, the relative weighting, the intensity, whether inhibitory processes are mobilized. These are all influenced by a lot of things.

So in the sense of keeping on track and allowing time for discussion, I was thinking, well, what can I also do. I don't know if you recognize this lady. She's a very important lady, and she was important in our family's life. She's a living author who said, "If we can have confidence in our decisions and launch enthusiastically into action without any doubts holding us back, we'll be able to achieve much more."

I'm quoting from her wonderful book called The Life Changing Magic of Tidying Up. It has to do with cleaning your house out and how that changes life.

Page 116

So I'm going to leave you with that note, and we can either start the next one early or do some questions afterwards. How would our mentors want to proceed? Take questions. Okay.

DR. TURK: A comment before I take questions. We were told by the transcriber, please talk into the microphone because she can't hear. So it's not just whether you can hear us, it's whether she can hear us in the transcribing. So even if it's awkward and you're turning around, try to use your microphone.

DR. CARR: Should I repeat my talk?

(Laughter.)

DR. CARR: But that's okay, I've rehearsed the spontaneous insights. So actually, I did have a spontaneous insight. Thanks to Dennis with his use of the analogy of the herd, that we are a herd, of course many people observed, including Aristotle, that we, man is a social animal, or people are social animals.

So if you think about this, there are many, many examples of pack animals or herds that when

Page 117

one of their members becomes wounded, or ill, for a brief period of time, they will be supportive. You know, these are like the things you see on YouTube where the elephants are trying to get the other elephant up and get it to walk and so on. But at a certain point, if that injured elephant can't continue with the migration and the herd has to get going, or can't help the wolf pack feed itself, the members of the herd turn on that animal and drive it away or even will attack it. There's a lot of examples of that.

So I don't know if this adds anything to the debate, but I was thinking in some implicit way, when we think about acute pain, we're probably thinking about that first phase where the member of the pack or the herd has been injured.

We're willing to put a lot of resources in. We're going to do fancy nerve blocks. We're going to use ultrasound guides. We're going to put an epidural, whatever. We're going to get that person through. But then I think as time persists, and the person doesn't reenter their functional role,

Page 118

they tend to get stigmatized, and there's certainly a large literature on stigma and pain. And they also stigmatize themselves.

I was intrigued by that quote from Steve Hyman that maybe this notion of depression and pain can -- maybe they're actually the same thing, that maybe there is a way of behaving where the person figuratively will crawl back into a cave and either get better and rejoin the herd or not get better and at least will not be a burden for the herd if they die off in some cave.

Maybe they're the same thing. And that's that second phase that we've been seeing in animals all the time, where the herd expels the animal, and the animal goes along with it and just slinks away quietly back into the shadows. So I think, to me, this is at some level resonant with the notion of acute versus chronic pain.

DR. TURK: Is that a cautionary note, Dan? Are you saying that if people don't go along with what we want, we're going to attack them?

(Laughter.)

Page 119

DR. CARR: That's a great idea. That's a good suggestion. I was thinking that you were going to say slink into the shadows. I don't know.

MALE SPEAKER: [Inaudible - off mic].

(Laughter.)

DR. CARR: Yeah. You mean lemmings? I don't know.

Henrik, this is the person we want to hear from.

DR. KEHLET: No, that was wonderful, Dan. But I think we only have two days to discuss the taxonomy of acute pain, and I simply think we should decide on a time frame for that acute pain and leave the question about transition to chronic pain.

That is too complicated, and I must admit, I think that your review on that was quite superficial. So I will suggest that we stay on acute pain and decide on a time frame and not going into persistent acute pain.

But I want to hear what you say. We have been in that area for so many years, it's so

Page 120

complicated.

DR. CARR: So when you say time frame, you're saying we should say acute pain is a new injury and it causes nociception for X number of days or hours?

DR. KEHLET: Yes.

DR. CARR: Would you make an opening bid about X?

(Laughter.)

DR. KEHLET: I would suggest something around one week. Because the further you get out, the more complicated it gets.

DR. CARR: Well, I certainly don't feel motivated to argue about it. It is incredibly complex, but I don't see why we couldn't try both. If we don't spend all our time working out complexities that are too difficult and we're never going to get done, but if we acknowledge that operationally we can take one week, it's not that different than saying chronic pain is whatever, 3 months or 6 months.

That doesn't undermine the motivation to

Page 121

study mechanisms of chronic pain, but you can do both. You can say in practice, we can say acute pain is a week.

Dr. Buckenmaier?

DR. BUCKENMAIER: Frustratingly, that approach of providing some sort of time frame that we're going to work in has been a real problem, particularly with the soldiers that I've been dealing with on the battlefield. It is a continuum. It is a process. I've recognized neuropathic symptoms in a fresh amputee literally hours after their injury.

So trying to compartmentalize and not look at pain as a disease process that has an acute and a chronic component, like [inaudible – mic fades] processes, makes it difficult to actually build a system then to manage it.

It's the silos that have literally been killing us in the military where we do things very effectively in the acute setting on the battlefield, but that provider never gets to see the consequences of that pain approach months or

Page 122

years down the road because that system wasn't established.

So decisions we made with opioids, very early on that made lots of sense in the acute setting as we're dealing with the trauma, that provider doesn't see the damning outcome as that opioid monkey is on the back of that soldier trying now to deal with his healed injuries but lifelong chronic pain that still makes him an unproductive citizen.

So I think we have to look at it as a spectrum, a continuum. And trying to part an artificial time frame on it only creates more problems than in my opinion are actually going to solve.

DR. CARR: Steve?

STEVE: Yeah. I think that's an acute condition that clearly looks like it's neuropathic pain. And then in our original AAPT for chronic pain, we've got neuropathic conditions that look a particular way. And presumably they would look pretty similar if they've got comparable underlying

Page 123

neuropathic mechanisms.

Since we have, by definition, set up a chronic pain and a separate acute pain taxonomy, it kind of leaves us with this challenging problem of having conditions that should look similar if they're both neuropathic, but we've said they're different, and we've arbitrarily dichotomized a continuum.

Pragmatically, we kind of have to do that, I think. And I guess the question is, just for future reference as we're thinking about this, is there a way to make that cutpoint, agreeing it's arbitrary, but making a cutpoint between acute and chronic in a way that makes sense that's flexible that doesn't box you into difficult situations like you're talking about.

So I think that is a really important issue that needs to be addressed in this. I don't think we're going to be able to totally avoid talking about time frames because somehow we're going to have to separate these from the chronic pain conditions. But I think that maybe there are ways

Page 124

of wording it to be flexible about it.

DR. CARR: Bob, we have a few -- everyone will be heard. Bob?

DR. DWORKIN: So the FDA sponsored a workshop I think about 4 or 5 years ago that some of us were at to address the question of extrapolation of efficacy from one acute or chronic pain condition to another. If a drug works in X, is it likely to also work in Y?

The consensus of that workshop was published, and in that piece on extrapolation, acute pain was defined as up to 30 days, and chronic pain was 90 days or longer. And that was done to be consistent with IASP.

Of course, that leaves a middle 2 months that we called subacute pain, not being very creative. That would be a starting point if we wanted to adhere to what is consistent with IASP, what is consistent with the FDA's way of thinking about these things. I'm not advocating for it, but it certainly is a way to start.

The only other thing I'd want to say is in

Page 125

the discussions that led up to this meeting, an additional dimension for acute pain that was proposed to add to the five that Roger discussed, would be a dimension that focused on the temporal aspects of the particular acute pain condition. So there would be a dimension that really discussed, for whatever acute pain condition, what are its temporal characteristics.

As Dennis mentioned earlier, the two of us know very little about acute pain, but the way I think about this is if we've got diagnostic criteria for renal colic, the temporal dimension is basically going to say that this is an acute condition that typically resolves and doesn't lead to chronic pain; whereas, for acute traumatic pain, surgical pain, et cetera, the temporal dimension would have a discussion of risk factors for chronicity.

So that would be one way to address the temporal aspects, which is to add a dimension that specifically describes those features when relevant.

Page 126

DR. CARR: Can I just ask you a question, and back to Henrik, and everyone else will be called on and have their say. But as long as the idea is in here, what would you do if there were a decision to make 30 days or 7 days? How would that fit into the big picture? Do you just say we're going to define acute pain as pain within X time? What would you do with that idea?

DR. DWORKIN: Well, what I would do, I think it depends on the condition. So the acute pain condition I think I know the most about is acute pain in patients with herpes zoster. So for that, I would think a week is a little too short. And if I was responsible for coming up with diagnostic criteria for acute pain in herpes zoster, I'd be thinking about pegging it either to the period until the rash is completely healed and there's been loss of all scabs or up to 3 to 4 weeks.

That would be a kind of mildly interesting discussion. Do you define acute shingles pain based on the rash or based on just what we know about the kind of epidemiology of the acute phase?

Page 127

And other conditions it might be no more than a week or hours, or perhaps in some conditions, it's hours.

So I think it would be condition specific. But I think once you get beyond 30 days, you're really kind of transitioning to a subacute chronicity kind of process.

DR. CARR: So let me ask Henrik, how would you have put that in the final document? Because if the document just said acute pain is pain lasting up to X days, let's say it was 30 not necessarily 7, then is that the end of it? And then what value has this enterprise added?

DR. KEHLET: No, no. It is no way the end of it, but we have to deal with the problems around acute early pain, and I thought that was the purpose of this meeting. Because if we go into the persistent thing, we would need another at least two days.

There are so many challenges in acute pain by categorizing patients, overlapping pain conditions, pre-op opioid users, all the

Page 128

psychological issues. And it has never been addressed in all these pain trials because people just say patients and pain and analgesics, and lump it all together. And the future will be to divide it up in different pain patients.

DR. CARR: Well, I see this is echoing what Roger was pointing out earlier, that we could be revolutionary and take a purely mechanistic state of the art, or evolutionary. And I think that AAPT succeeded in introducing new important valuable content in an evolutionary way. Maybe we'll do the same thing. I'm not sure.

There are a lot of people that have questions. Bob, did you have one other thing to add? And then we'll start getting all the hands?

DR. DWORKIN: I just wanted to say I completely agree with Henrik. If I'm doing a clinical trial to look and see whether pregablin is efficacious for acute pain in patients with herpes zoster, I don't need to think about PHN.

I could have a dimension in my diagnostic criteria that some patients with shingles develop

Page 129

PHN, but for my inclusion and exclusion criteria for a study of whatever drug for acute pain in zoster, I don't need to think about PHN. So in that sense I completely agree with Henrik.

DR. CARR: Okay. But before getting the hands, I would say that what if we were having this conversation about placebo? In other words, what if we decided that not addressing whether a proposed enrollee in a clinical trial was a placebo responder or not might impair the quality of the trial or our ability to detect --

What if these other things that we're lumping as psychological factors, what if they had an equally great magnitude upon ultimately the effect size of the trial? Maybe it's time to dig a little deeper and bring those out into the sunlight.

DR. DWORKIN: But that's still the acute -- that's a question of for my trial of zoster, do I include individuals who are depressed, but that still has nothing to do with the chronification. That's, you know, during their

Page 130

shingles are they depressed, are they catastrophizers, and maybe I want to exclude those to improve my assay sensitivity.

I don't think Henrik would disagree that if you're doing a trial of acute post-operative pain, you want to pay a lot of attention to the patients' mood and physical function, but you don't necessarily need to take into account the risk of the patient still having pain 6 months later.

DR. CARR: Okay, there were a number of hands up, so now as promised we're going to go around. Yes, please?

DR. SCHREIBER: So I was just going to say from a clinical standpoint, we are still concerned about chronification of pain in that we know the acute pain is going to end, and obviously we want to treat that, but I think there's a great amount of importance about whether it becomes chronic.

I mean, if it's a separate discussion and a separate interest group, then it is, but I think it is a really important thing. And it will guide our treatment of the patients, like say in the

Page 131

perioperative period. You know, like do I want to give this person -- are they going to respond to X drug in terms of preventing chronic pain? It's an important question, but maybe a separate one from whether it's going to impact their acute pain.

DR. CARR: Let's see. Srini, then Deb, Sean, Dr. Edwards, and then we'll get over to this side of the room.

DR. RAJA: Dan, your initial title said key distinctions among acute, subacute, and chronic, so to respond to this duration question, in your opinion, when does acute become subacute?

DR. CARR: You know, you saw that I avoided that issue because I was propagandizing for the continuum. Yes, there's some he doesn't know, I don't know. I mean, when does acute become subacute, I don't know. I think the word "subacute" is a word that we apply to kind of patch a gap without much thinking about it.

We could retrofit some definition around the word "subacute," but it would be some derivative of a derivative of a hypothesis. You know, it would

Page 132

be the pain between acute and chronic.

So I think in subacute, the concept we have is that there's some organizing process, which is continuing to follow that initial injury, and it's either going to go back to baseline or go off in its direction of chronification.

To Kristin's point, though, I think we often are confronted with patients that are prevented from being discharged because their pain intensity is too high. So the pain trajectory, even acutely as our friends in PAIN OUT have seen, is a pretty good predictor in many instances of chronification, and it's very practical. It's not like you can think about it later because the problem is already there right now. I don't know if you want to add something, Srini.

DR. RAJA: No, I think the reason I was thinking of is you can define the duration of acute pain as pain that either resolves or becomes subacute. And the question is, what is that duration.

DR. CARR: Okay, we'll leave the question on

Page 133

the floor. And we said we would have a few other people, so it's Deb next, and then Sean, and then Dr. Edwards.

MS. GORDON: Thanks, Dan, for your talk. There's a lot in there. I mean, I want to agree with Henrik that I think we do have to continually stay within scope of what we can achieve, but I don't think we can completely separate it.

I'm thinking of all the work we're all doing right now to kind of identify complex pain patients in the pre-anesthesia clinic and doing catastrophizing screening, and resiliency screening, and looking at prevention. I mean, you mentioned prevention is so unique about acute pain, but part of the goal of acute pain is preventing chronic pain.

So that issue about expectation setting and intervention on the psychosocial factors, the pre-habilitation, the categorization of patients before they come to a planned surgery, and then how you quickly get them through that acute phase and prevent subchronic persistent pain. I just think

Page 134

it's going to be -- it's going to stick together.

DR. CARR: Okay. Sean? And by the way, Dennis informed me we'll maybe in the overall discussion period take questions from this side just to stay on track time-wise.

DR. MACKEY: I want to acknowledge the tensions of what I'm hearing from Henrik, who I agree with. We don't have it figured out. There's so many questions that we have, and at the same time highly support what you're saying in this continuum of pain. These arbitrary distinctions between acute and chronic probably just don't [inaudible – mic fades] and want to advocate strongly that we allow a classification system that will allow us to capture that continuum, so that we can better understand what Henrik has so eloquently stated.

Much like in the pediatric pain realm, we're all appreciating the developmental aspects of pain, and there's great efforts now to try to understand that developmental progress from when these kids have chronic pain into adulthood.

Page 135

We want to be able to characterize when people have acute pain and move into chronic pain. So parallelism with this group's effort with what has been done in chronic pain I think would be incredibly important.

Secondly, it would allow us, if we did align and have parallelism, to be able to better classify that patient who comes into the surgical or acute pain setting who has chronic pain, to classify that person's chronic pain and at the same time characterize the acute pain in that episode.

DR. CARR: Okay. Dr. Edwards, last question.

DR. EDWARDS: Sure, Sean said it greatly. I was just thinking practically when we have patients present to us, they're going to present somewhere along the continuum, not at the beginning in a research model, but 7 days, 12 days into an acute, subacute pain episode.

To be helpful to non-pain specialists, that's always the question, they never know who to consult. Do they consult a chronic pain service or

Page 136

an acute pain service, and what stage. And we help them define what stage this patient's at. So if we can't come up with some kind of plan for this at the outcome of this meeting, that's going to continue to plague us. Thanks.

DR. CARR: Thank you. I think those questions are -- there will be a lot of time that's built in already to discuss and handle further questions. We just can't handle right now because we have to move on to the next speaker.

DR. TURK: Thank you. It's great to have the questions. And the fact that we actually have more questions than time is perfect because what that means is that you're engaged, and you're interested, and there are a lot of things to work out. The worst meeting I've ever had was we said are there any questions, and we sat there for 45 minutes and no one said a word. So that's not very helpful.

Now, I'm going to go to our next topic, and there will be opportunities, as Dan implied, for discussion. This is not over. This is just

Page 137

weighing out some of the issues that you're going to be wrestling with over the next day and a half.

Going to our next speaker -- and we're a few minutes behind, but don't worry about that -- Tim Brennan. Most of you know Dr. Brennan, or Professor Brennan I should say, from the University of Iowa. He is a professor there as well as the vice chair for research. And he's going to give us a little bit of pathophysiology of acute pain with a question mark at the end, I notice. So let's see what he has to tell us.

Presentation – Tim Brennan

DR. BRENNAN: So when Dennis and Bob asked me to give this talk, and they talked about our meeting getting together, they talked about creating a straw man, so I will throw out the first bit of straw here.

My talk, I was given this topic. I created a little bit of a template of slides and sent them out. It's biased towards post-operative pain because those are most of the patients I see as well as post-traumatic pain. And I do basic

Page 138

research and am familiar with mechanisms and mechanistic research.

Bob sent me the mechanistic preprint from the chronic pain working group. No help. I could have picked up a textbook, read all the mechanistic work and the latest review article on mechanism, and I refrained from doing that. So I put this, sort of off the top of my head, but 25 years of acute pain and 25 years of pain research. Here it goes.

The conclusion, I'll begin with a conclusion that not very easily can we use mechanisms to classify acute pain, or let's take the other side to this and say we're part way there, and we need more information.

I think Kris included procedural, so we're going to review some pain mechanisms from Brennan's point of view off the top of his head. There's a few references in here, but there's not many.

So Kris mentioned procedural pain, that may help us a little bit, and I'm going to talk about acute pain. What am I going to talk about? We can

Page 139

take nociceptive mechanisms, neuropathic, inflammatory, et cetera. We can say, oh, it's sensitization. That's how we're going to characterize acute pain. That's how we're going to categorize it.

No, we're going to do it by mediators. This condition has factor Z, the other condition it's not there. Now, let's look at treatment. We got a drug; completely eliminates that acute pain problem, and that drug is totally ineffective in another acute pain problem, or we're going to look at tissue injured.

So with respect to procedural pain, I called it nociceptive pain. Treatment is local, and it involves peripheral nociceptor activation and central nervous system nociceptive pathway activation. I put a time on there as minutes. Let's get it on the table now. It can involve freezing or a burn lesion, it can be involved in injection. Those of us over 50 know distention for a gastroenterologic procedure.

It usually involves transduction of heat;

Page 140

you know we can burn things. Cold. We can use cold, nociceptive cold for procedures, and mechanical stimuli like distention or injection. And it involves transmission through both peripheral and central nociceptive pathways. And is not pathophysiologic, but we used our Levin's review article. We used our transduction mechanisms in acute pain. But it's not pathophysiologic, so let's take some pathophysiologic pain mechanisms and see where this going to get us.

Now, if we're going to be -- we've got time, we thought we had time to separate acute and chronic pain, but we haven't gotten there yet. And when I look at these mechanisms, I'm going to refer back a little bit to chronic because the time may be a little bit muddled, as you've just said. But if we've got these acute pain mechanisms, are they really unique and different than chronic pain, and how are we going to use them.

So here's the start. We can take our nociceptive mechanisms, mechanical, heat, cold, and

Page 141

I added chemical, and they transduce these acute stimuli, so we could say a sharp needle, something burning, ice, holding ice in your hand for a long time.

Chemical is a little bit ignored, but lemon juice in your eye is acid, and it's extremely painful. So we do transduce chemical stimuli as well. Neuropathic, I just said that's caused by nerve injury and inflammatory.

I put immune-mediating. Basic scientists in pain have overstated and over utilized inflammation, so everybody injects something that's brutally inflammatory and says, well, it's present in chronic pain, therefore we're studying chronic pain. And this in pain mechanisms, I think the pain research field has taken this broad inflammatory topic and said as is good for all of us, formalin causes inflammation, look at it, it's bad.

But this is a tough one because we've got immunologists who are very detail oriented and have markedly affected their pain patients, but we've

Page 142

used it really broadly. And I left it immune-mediated, and we'll move on to that.

I could pick an example. Swelling after a sprain, maybe even throbbing, nociceptive or ischemia. If you've seen my slides, I'm going to throw out ischemia as a mechanism not well appreciated.

We talked about seeing acute neuropathic pain. We know we cut, stretch, and inflame nerves during injury, trauma, surgery, et cetera. And we can find acute inflammatory conditions, and I put an easy one out there for me because I'm talking off on my own here without reading any of the rheumatology literature.

But almost all of these, as I'm going to show you, are components of acute pain condition. We may not recognize neuropathic pain, but nerves are cut, and we're not exactly sure of the consequences.

So let's keep going in the detail here. We think that nociceptive mechanical is an important part of acute pain mechanisms. I mentioned

Page 143

swelling. We can get release with elevation and reducing swelling. It must be there. When we take a deep breath after abdominal surgery, we stretch the abdominal muscles. It's notable to be pain and so stretch or a mechanical component is clearly evident in acute pain. And if we cough, we contract the middle of the muscle and stretch the outer part of the muscle and also can produce pain.

So any evoked pain with activities has a mechanical nociceptive component, and most acute pain we think has evoked components, as Henrik taught us in the early '80s and '90s.

So chemical is understated. I put ischemia as an example of chemical transduction in pathophysiologic mechanisms, and I put hypoxic lactic acidosis in as an example of a chemical transmission. Compartment syndrome after trauma. That's great, so I've got an ischemic condition there. We can put that into our category, but I'll tell you that that mechanism looks to be operative with fracture and bone remodeling.

I showed almost none of my own slides from

Page 144

my usual lectures on acute pain mechanisms, but I threw a few in at the end to show you wounding, loss of blood flow, and coagulation will produce this ischemic mechanism, and of course, it occurs during a heart attack as well.

But when the NGF trials came out in osteoarthritis, I listened to someone lecture about osteoarthritis, that mechanism is also present there. If I get this wrong, please correct me, but endochondral bone has no nerves or blood vessels. When it becomes inflamed, there's high oxygen consumption, inflammation, neovascularization, new innervation, and pain from osteoarthritis.

So I went back to chronic pain, not my intention to overlap, but we'd love to have specific acute pain mechanisms. When I was working on ours that I'll show you a little bit of information, I was struck by the osteoarthritis literature.

So I think Trip mentioned acute neuropathic pain. Henrik told me a couple years ago, oh yes, there is acute neuropathic pain in surgery,

Page 145

surgical and traumatic nerve injury, so there are some studies on thoracotomyne, acute zoster. Phantom at least must be acute -- acute phantom must be neuropathic. Inguinal hernia, iliac bone harvest are others hypothesized to be acute neuropathic pain.

All trauma has nerve injury to some degree. Every time, usually tissue is innervated and nerves are cut, and its role in acute pain I'd say is noted. We think that's there and that's present. I'm a little bit -- I'm going to struggle that using a neuropathic pain scale in the acute post-operative period is demonstrating that a patient has neuropathic pain, but the literature is sort of moving this direction. Certainly, the acute phantom; we'd have to give them that.

I really struggle with the broad term of inflammation, but it's generated a huge amount of basic science, research on pain and pain mechanisms. Almost any tissue injury or trauma is associated with some form of inflammation. We could talk about inflammation using markers. We

Page 146

can talk about it as leukocytes, and we can talk about it as TNF.

So I actually threw out a few references here to talk about a variable role of inflammation in post-operative pain. I'll begin with a meta-analysis on dexamethasone for Northwestern that basically said it's a mixed effect, and I'll come back to treatments, and I'll be redundant in some of the information.

If you look at NSAIDs in COX-2 inhibitor trials, you can look at -- here's a recent intravenous ibuprofen trial that was really weak for any benefit in open abdominal hysterectomy. And I think Henrik's database website recommended specific treatments for specific surgeries that I think was in agreement with this weak effect of, in this case of an NSAID.

If we look at parecoxib in hip replacement, we'd say there's a moderate to strong effect. And if we looked at the dental literature and third molar extraction, I reach back to 1986 in which they showed a strong effect of NSAIDs in the dental

Page 147

literature.

I'll just point out a TNF's inhibitor high utility in autoimmune acute pain conditions. I think maybe we'll touch on that tomorrow. And certainly it has a role in acute joint infection.

Bob would go back -- we could go back and forth on whether acute zoster is inflammatory or whether it's neuropathic or certainly a combination, but you can see that these injuries are multifactorial and redundant and use a variety of mechanisms. And who is to say a simple surgical incision through the abdomen doesn't have all nociceptive components, neuropathic, and inflammatory components to it. Thus, the categorization of pain mechanisms is all inclusive.

So I put mechanical and chemical, and I dropped heat and cold. They are great for modeling the pain system and categorizing nociceptors, but I don't think -- we can argue this after lunch -- that those are really stimuli we're really interested in, in acute pain management.

Injury occurs throughout. We think acute

Page 148

neuropathic injury exists but is not consistently diagnosed. And it's difficult to diagnose. I really struggle with the neuropathic surveys as their use in the acute pain period. I had a burn surgeon come up to me and say, I gave the LANSS scale to all my burn patients, and they've all got neuropathic pain. And I winced and kept it to myself.

Immune-mediated responses are common, and we can get some separation if we pay attention to the rheumatologists and their autoimmune conditions.

Okay. We're all excited about sensitization, and I hear, not infrequently, acute pain, well, that's peripheral sensitization, and chronic pain, certainly that's central sensitization. And going to the IASP definitions -- I just put them up there as a reminder of increased responsiveness of nociceptors -- central sensitization was broadened by ISAP. I call this recent. When you've been around a long time, 2008 is recent, but it is increased responsiveness of any part of the central

Page 149

nervous system nociceptive pathway.
I read the Hopkins article, Raj was included in that, and they called, true central sensitization, and it was inspiring to read, a really rigorous characterization of central sensitization.
So Dan, I stayed broad, but acute pain minutes to weeks, we'll throw it out there. That's good. And in the sensitization, I said early acute pain, off the top of my head, as high local amounts of pain mediators and sensitizing agents, and a prominent peripheral nociceptor activation and sensitization. However, with the broad definition by the IASP that anything activated in the central nervous system is now central sensitization, using the very broad definition, this is occurring as it makes its way up to the central nervous system.
I'm going to posit that in chronic pain -- I'll put it out there. Chase me down at lunch if you disagree -- there are less local mediators in chronic pain conditions, but nevertheless, it's still peripherally maintained.

Page 150

We do trigger points in myofascial pain. We get a pretty good response.
I threw out , I think chronic pain, a lot of chronic pain has structural problems rather than mediator problems, neuromas. Steve mentioned tendinopathy. I'm glad he did that as we're onboard. But central sensitization may be more prominent in chronic pain than acute pain. And I think I was hurt [indiscernible] -- did nerve blocks on upper extremity phantom and had a 50 percent response rate.
So we still can't get far from chronic pain with this sensitization topic. There is central sensitization in acute pain. The area of secondary hyperalgesia is one surrogate of central sensitization. It's only one, and it has a limited clinical relevance. Certainly in the acute pain setting, we can talk about central sensitization's engagement of affect of anything supraspinal. I'll leave it at that.
Acute phantom pain may have a strong component of central sensitization. And I think I

Page 151

was worried about too many slides, but every time somebody's getting a shoulder replacement, and they get a nerve catheter, and we dose it up with local anesthetic, it relieves their chronic pain almost invariably. So even using peripheral versus central sensitization as something to try to define our acute pain doesn't separate, even difficult to separate from chronic pain.
Most acute pain is strongly driven by peripheral sensitization, certainly in days, maybe up to weeks. The importance of peripheral sensitization even in chronic pain patients prevents using it I think or makes it very difficult to categorize acute pain. And the role of central sensitization, we already threw that out there. I think it's central, et cetera, and chronic pain is an area of active study by Roger and others.
Okay. I didn't get too far with pain mechanisms. This is up for discussion, but I don't have very far to go. But certainly, if we can find a mediator that's generated in one condition but

Page 152

not another, we can maybe classify our acute pain.
So I did go pick one of these articles like John Levin had the lists of mediators. I don't remember if this was dental or not. And these are -- if we're doing basic science, if we're doing that, we need to recognize our limitations. So I changed theirs to hypothesized mediators, and they're redundant in various acute pain states.
So well, prostaglandin, that's a good one, and I struggle with histamine. But CGRP, NGF, all these, substance P, we've thrown out these. You can pick up a review article. We're still there in all these mediators. But at least I tried. Come back and challenge me after lunch.
Clinically evident mediators in human studies, we could go with prostaglandins, and I said acute pain states. We'll go with prostaglandins. If you'll bear with me, I think Pfizer did some trials in acute pain that had some markers in there, a little bit of a signal there.
Polycytokines, I haven't seen it, maybe you have. Nitric oxide, bradykinin, the darling

Page 153

molecule of the '80s. Platelet activating factor, wonderful. TNF-alpha, not in acute pain. So everybody, all the rheumatoid arthritis patients who come in loaded with their TNF-alpha don't come back and say, you don't even need to see me, I don't have any acute pain. It must be my infliximab that I'm taking. It's completely eliminated my acute pain. I don't see anything there; maybe you do. But TNF-alpha in acute pain states, unless it's an acute rheumatologic condition, is different.

Substance P, no, didn't make the clinical trials. Give me this for migraine at least; that looks positive. ATP acid and lactate, those are mine I added at the end. Not a lot of attention in that area.

So can we classify things based on pain mediators? pH lactate, there is some human data in there that this ischemic like signal may be present. I'll talk a little bit more about it. It's present in incisions and, again, there's human data there. Present in compartment syndromes.

Page 154

Tourniquet induced pain has this.

But I mention that this is present in OA. And if you read some review articles on cancer pain mechanisms, the tumor grows fast, outstrips its vascular supply. Tumor cells love lactate, so they're very good lactate consumers. We need new vessels. When you make new vessels, nerves follow, so that gets hyperinnervated and maybe is something we're talking about for a cancer pain mechanism.

So this I think is important. It's my own self-promotion here in pain mechanisms, but recognize that it's present in other clinical conditions that aren't even in acute.

NGF, we've studied this. Incisions, it's present in humans in burns. It made the OA trials there for this sort of scenario and is certainly effective and went to bone cancer trials. I think they were held up, but reasonable that this neoinnervation that follows blood vessels is an NGF dependent process.

The neovascularization appears. NGF appears to play some role in that. If you do enough

Page 155

patients, the neovascularization doesn't go well, and you end up holding the NGF trials for dead bone, apparently, or linked, or let's say associated for now.

Prostaglandins, we'd say OA, incisions of soft tissue injury, and certainly the dental is strong for prostaglandins. But there's a lot of overlap, and we're going to struggle to do that.

So I said I'd show a few of my own slides, and I'll begin with, in acute traumatic pain, monocytes are called to the wound immediately by a change in ReDoc status in traumatic tissue. So there's trauma, and immediately the ReDoc status of the tissue changes, generates peroxide. And according to wound-healing literature that I think I understand, immediately the monocytes and macrophages go into the wound.

Macrophages can generate the acid lactate. We've lost blood supply. The macrophages can survive that. They like to generate lactate. Wounds are hypoxic to stimulate neovascularization. Nerves are cut. The yellow ones are cut. The red

Page 156

ones survive. So the red ones can respond to this example of perhaps a signature for a variety of pain conditions.

The difficulty in -- and this may occur in myocardial ischemia in part, so let's be careful. And just one example of that high peripheral mediator, strong peripheral sensitization.

So in my opinion, acute and chronic pain diseases share many of the same mediators. In acute pain, trauma coagulation monocyte activation produce a local environment for revascularization, reinnervation, and a hostile environment for bacteria, geared up environment for an immune-mediated response to clean up the dead cells, clean up bacteria.

That tissue, that local tissue repair, the surgeons who study wound healing study the skin. That same process is occurring in deep tissue and we think is a very good pain generator. But that repair process when transduced in nociceptors contributes to pain, that process is redundant in osteoarthritis and cancer as well, I think.

Page 157

So lunch is ready. Let's try two more categories. Treatment, drug A is effective in condition A but ineffective in condition B. Unfortunately, gabapentin sort of became the broad spectrum analgesic. When it came out, we said it was an anti-neuralgic. We use it in total joint replacements, breast surgery, and spine surgery.

Cyclooxygenase 2 inhibitors are good in the perioperative period for orthopedic and neurologic surgery. Maybe we get a little separation because they're less remarkable in thoracic and gynecologic surgery.

I showed you glucocorticoids look to be a little bit better in laparoscopic hysterectomy and cholecystectomy and less effective when the surgery opens and becomes major.

I think Deb brought up in an email, bisphosphonates have fair specificity for bone related pain I think by impairing osteoclast activation, which creates that high acid environment for bone resorption.

So we can get some specificity, I think,

Page 158

because if you study the autoimmune phenomenon, and drug companies have sort of gone okay, we've got this, this and this, these are all conditions that have been approved -- these are all drugs that have been approved in these autoimmune conditions.

So if we can talk about acute autoimmune conditions, we can separate ourselves out with these drugs because I think they found very little utility in other conditions, at least they haven't been approved yet. And I think a part of an issue is the pain field has viewed this as inflammation, and that's chronic pain, but it's a specific inflammatory pathway. The rheumatologists capitalized on it and have done a remarkable job. And we, in looking at etiology, aren't so good.

Someone asked me one time -- I gave the TNF inhibitors in our incisional pain model. NGF inhibitors worked, TNF inhibitors didn't work. And they asked me what did I do wrong because it didn't work. And I knew that the rheumatoid arthritis patient, at least an acute one, has a totally different response to a group of medications that

Page 159

acute pain patients do not respond to. So there's a little bit of specificity here.

Many acute and chronic disease states share the same treatments. COX-2 inhibitors have broad efficacy, but appear to be stronger in orthopedic related acute pain conditions, and I think Chris is mentioning this tomorrow when he talks about post-operative pain. We've got some specificity there if we want to include autoimmune conditions.

This is my last hope. I saved it for last. Tissue injured. So there are tissue-specific responses to acute injury. And I think I'll posit it's always a model that skin responds different than ligament, that responds different than bone, than vasculature that's injured, joint that's injured, viscera that's injured, nerve that's injured, or the dental area that's injured. They respond differently to injury.

So I said here, off the top of my head, if someone does a small skin incision on my foot, it's cutaneous injury, it's not too bad. I'm going to have some hyperalgesia if I walk on it. But at

Page 160

least by my observing others who've had plantar fascia release at that same area, they struggle to walk for weeks and have a pretty significant amount of hyperalgesia, long-lasting and of greater intensity.

So we've gone skin, skin and fascia, and let's add bone. But if we do a hip replacement now we've injured skin, and we've injured fascia, we've injured muscle, we've injured ligament, and we've injured bone, and that produces a much greater intensity of response.

Pick a different surgery, we injure skin, we injure fascia, we injure muscle. Let's include the peritoneum. I think there's a little bit of literature that if we deep, local anesthesia has high efficacy. And then we injure the viscera, and we don't understand that well.

On the acute pain service, sometimes someone will be scheduled for an eight-hour Whipple. It's open and close. You have to be careful when you're rounding because you go and see them, and it's noon, and they're done, and they look great because

Page 161

they had a 1-hour surgery, not an 8-hour surgery. Less injury here, less retraction of muscle and fascia, but those seem to be components to that.

So tissue transduction does -- I guess I'm a little bit self-promoting here -- but does have some specificity, differences in visceral afferents and what they're expressing. Subchondral bone afferents have a lot of the NGF receptor, which made them useful in the OA trials.

We have nociceptive markers that are associated with tissue signatures that may not be causal, but I'm optimistic. My favorite is tissue injured.

If we want to look at mechanism -- this is a slide a graduate student dug out for me on hip replacement patients. There is pain at rest. In two different studies from the same journal, from different organizations, they did a non-invasive hip surgery, and then the surgeon got permission to extend the skin, to double the size of the skin incision. There was no difference in pain and opioid consumption.

Page 162

If they did the minimally invasive surgery, different group, versus dividing tendon, muscle, ligament and fascia, they had greater pain and greater opioid consumption with more fascia muscle and ligament injury.

So there is evidence, at least I like to think, I'm biased, of tissue specific mediators, receptors and responses. The skin is great for studying heat and mechanical hyperalgesia in rodents, but deep tissue likely generates clinical pain, at least if you'll buy the previous slide.

Acute ischemic pain appears to be a muscular pain rather than a cutaneous pain. Someone thromboses, their propliteal artery, they've got cramping in their muscle, usually not complaining about the skin, and changing the degree of cutaneous injury has little effect.

Acute pain and repair, it's linked to neovascularization. Repair mechanisms vary with tissue. The repair people are ahead of the pain people. But there's also redundancy. There's this receptor that we think is a pain mediator present

Page 163

in joint, viscera, muscle, and skin. In the trachea, may mediate some asthma, not pain, but in muscle it may mediate pain, for example.

So I already concluded at the beginning of the talk, and now I'll conclude again, can these mechanisms inform classification of acute pain conditions? And the first thing I'll say is, not very easily. The cup is a quarter full. We don't have sufficient information. We need the other three-quarters.

In my opinion, my straw, throwing down the first straw of the meeting for Bob's straw man, the best opportunity for pathophysiologic classification may be in the types of tissue injured. Thank you.

(Applause.

DR. BRENNAN: Do you want to go straight to lunch? Okay. Fire. Bring it on. Henrik?

DR. KEHLET: I think this was a very eloquent talk, and it clearly argumented for us to focus on the early acute pain phase.

(Laughter.)

Page 164

DR. BRENNAN: It's so difficult to dissect different acute pain states. Other than time to separate acute and chronic, the pain system needs some really good pathways to work well, to be linked to wound healing, to be linked to alarming systems. And so it can use the same ones in both acute and chronic pain states.

Yes, Suresh?

DR. SURESH: So Tim, thank you very much for this talk. An other question that will come up, and I think will come up in discussions further, is what happens with acute on chronic pain? Are the mediators going to be different as opposed to the mediators for chronic pain alone? We have a whole group of these individuals who are coming back for surgery, et cetera, and how do we deal with them?

DR. BRENNAN: I'm going to say the mediators aren't -- I won't expect the mediators in the peripheral tissue to be profound in chronic pain states. If there's a chronic infection there, you're going to find that. But when we've looked for what are the mediators and trigger points, you

Page 165

can't find them.
I think it's become scarred, maybe from healing, and maybe it's structural, or it's hyperinnervated. I'll throw that out as one of the ways chronic pain distinguishes from acute pain. So I don't think they're there. I think they disappear as neovascularization develops.
Yes, Greg?
DR. TERMAN: I'm not sure it's relevant, but I'd be interested in a couple of words on allodynia. Your definition of central sensitization sounded a lot more like hyperalgesia than allodynia, just because of responding more but in a normal -- to the normal stimuli.
DR. BRENNAN: I think the IASP kind of put allodynia and hyperalgesia on a continuum on that 2008 definition. So I think they kind of just said it's all hyperalgesia throughout the spectrum of stimuli. I thought -- and anyone else can comment, but I thought that was the case. And they broadened central sensitization quite a bit. So we could all study central sensitization because once

Page 166

it gets past the afferent, it's all central.
MALE SPEAKER: Thanks for a good talk. I really like the point about starting with tissue injury because since we spent the morning -- I'll admit, and I don't want to throw tomorrow on its head, but I'm having a real tough time with the 5 dimensions and trying to fit broad stroke acute pain states into the 5 dimensions.
Pat's probably going to be talking after lunch, and I think it's going to be a great follow-up talk to yours, because I'm almost wondering -- and I know it's going to come up on the discussion this afternoon probably, is do we just need to not throw out the dimensions, but completely or at least consider redefining them in terms of acute pain? And I think a good discussion point later today would be is tissue injury actually the first dimension we should start with.
I purely conceptualize it in my head, but just wanted to throw that out there because I'm sure that topic is going to come up for conversation in terms of redoing all the dimensions

Page 167

to fit a better acute pain state. I hear your point, and I think tissue injury should be discussed, and I think that might be a good pure place to start with.
DR. BRENNAN: Okay. Noted.
Yes. All right.
DR. TURK: So if there are no more questions, we'll break for an hour for lunch. One announcement. We've changed the agenda. So at 1:00, Patrick will be giving his talk. That will be followed at 1:45 by Steve Bruehl giving the talk he was going to give tomorrow afternoon, but we've upgraded it to this afternoon. Then there will be a coffee break at 2:30, and 3:00 until midnight will be the panel discussion and Q&A.
(Laughter.)
(Whereupon, at 11:58 a.m., a lunch recess was taken.)

Page 168

A F T E R N O O N S E S S I O N
(1:12 p.m.)
DR. CARR: All right. Can you all hear me? The mic is working? What I'm going to do is get us going. We're a few minutes late, but we'll pick up the slack, and we should be back on schedule before long.
As you heard this morning, at the end of the morning session, we're switching the sequences a little bit. So it seemed to make more sense to get more foundational work and throw out some more fundamental ideas.
I've known Patrick for several years, and he is absolutely an idea person who brings expertise in mathematical modeling and almost philosophy, if you will, to the issue of acute pain and big data, how to manipulate it, and how to data mine, and so on.
So I'm very much looking forward to the talk. I had a sneak preview, and I thought it was tremendously thought provoking. So Patrick, the stand is yours.

Page 169

Presentation – Patrick Tighe
DR. TIGHE: Hi there. Good afternoon, everybody. Can everybody hear me okay? Fantastic.
My name is Patrick Tighe. I am an anesthesiologist at the University of Florida, and we're going to talk a little bit this afternoon about towards the taxonomy of acute pain conditions, lumping versus splitting and other general considerations.
Now, this is a little bit different in that we're not going to be focused directly on pain itself, but really more the organization of information as we look at how best to organize our ontologies or taxonomies.
For disclosures, I have no financial conflicts of interest to report. The most important non-financial conflict of interest is my family, mentors, collaborators and colleagues. This is truly a team effort, and there's no way we could have done any of this work even with just a portion of the wonderful support system we have behind us.

Page 170

The three topics we're going to go over today, first we'll go over the need for ontologies and why this is so important. We'll look at something called schema architectures, which is different ways we can organize how we approach this group to give information about pain. And finally, we'll talk about the potential applications to the actions I mentioned that we've discussed so far this morning.
So the need for ontologies, we need these now more than ever. But I'd like to start by defining a few terms, and the first is a vocabulary. Well a vocabulary in this sense is a very specific connotation. It's a list of terms that don't really carry any context.
There's no organizational schema to this. Blue, pizza, bubble, beach, red, hamburger, you might be able to infer some similarity between the concept of hamburger and pizza, but aside from this, just a wash. It's a flat listing. There's no organization whatsoever.
So how does this differ from a taxonomy?

Page 171

The taxonomy is an organizational listing of items in tree form. As most of us learned at some point in school, we have kingdom, phylum, class, order, family, genus, species. This is how we organize organisms in terms of some type of classification. Notice this is generally quite linear, and generally a species is a member of single genus, which is a member of a single family, et cetera. There is not a lot of overlap here.
So this fits very well into the organizational structures we've tried to use already today, where we take one concept of pain and try and lump it into a single organizational structure whatsoever.
This is incredibly helpful. These are very valuable in any types of classification schema. It's typified by a tree structure. And we see here a relatively simple structure. We have one parent and multiple children. But in general, we don't see multiple children belonging to multiple parents. It's usually a one-to-one type of matching going from bottom up.

Page 172

This differs a fair bit from an ontology, where we look at organizing a multifaceted complex collection of relationships, and I have a wonderful definition here courtesy of Wikipedia. But really what's important is this allows us to interconnect what would otherwise be different conceptual mappings.
So now, with an ontology, I can map and define all sorts of pain related concepts, and I can relate it to other domains, such as health policy, or education. And I can begin networking things together.
Interestingly, this is the approach that a lot of our computer science and database folks of latched onto because it allows them to have a very robust structure. And when we organize data in this methodology, we can then leverage it, we can do things with it, we can operate on it, and it enables a much stronger sense of research.
So what does that look like? Well, we talked previously in taxonomy about a general ontology, or a general tree structure. And we see

Page 173

here an ontology that were much more different.
We still have elements of a tree structure, but we can separate out to a number of different areas, and some of these can actually be interrelated. So there was a discussion earlier about a patient with bone pain from a sickle crisis, and we see here that an ontologic representation allows us to link children together, even across what would appear to be relatively different superordinate settings.
So now I can have a method of measuring blood pressure, such as arterial line, and we can also refer to it as the type of site that we're using it. Is that femoral? Is that arterial line in the aorta, or perhaps femoral, or radial, or others?
Another important feature of this is that we can take our blood pressure and link it to heart rate. And this is obviously a very dynamic, complex relationship in physiology. But we now have a schema to look at how these two concepts can interrelate with one another.

Page 174

It's much more than just a tree-like structure. It enables us to have a lot more flexibility to map what I think a lot of us intuit from our different perspectives of how this constellation of observations of a patient who is suffering from pain, how we can begin to try and niche it out into our own organizational perspective and maybe objectify it a little bit further.
Why are they so important now? Well, I would say three simple words, "electronic medical records." We had a research protocol a little while ago that we simply said, hey, we'd like to look at the blood pressure for patients after surgery. And they said, okay, what kind of blood pressure? And we said, well, their blood pressure?
(Laughter.)
DR. TIGHE: They said what kind of blood pressure? What do mean? Well, would you like their systolic and diastolic? Well, yes, oh yes, systolic and diastolic and mean. From which site? Either arm should be okay. Is a leg okay? Well I

Page 175

guess that's okay, too.
Thirty minutes later, we were still having a discussion about what kind of blood pressures we wanted, before and after surgery, just after surgery. What if there was discordance? What if we had two measurements within 3 minutes of each other? What if they were different?
It turns out that for something that I thought was as simple as blood pressure, it's an incredibly rich representation of concepts that we need to map out. And it's not just for a research purpose, for blood pressure. It's not even for a diagnostic purpose. It's actually so we can enable the operation of our clinical enterprise.
Our electronic medical records depend upon an accurate organization of the information; otherwise I don't know what I'm putting down in the record, and I don't know what I'm reading when I go to make a medical decision. So it's even more fundamental than establishing research and clinical diagnoses. It actually enables us to provide a substrate with which to build a research enterprise

Page 176

and to build a clinical enterprise.
What does that value mean I think is one of the core tenets that we've run into with ontologies. When somebody tells me they're in pain, what does that mean? There's some discussion of validity and such, but this becomes very concrete when we're looking at medical records and other databases.
When you say that this patient has acute pain after a total knee arthroplasty, how do I know that you mean a tri-compartmental knee arthroplasty versus a uni-compartmental knee arthroplasty? We have to be very concrete and specific.
We also have to be able to roll things up. And this requires us to start defining variables, in some cases by other variables. It's like an algebra of organization. I don't necessarily even need to know what the exact term is, I just need to know what the representations are in some cases.
But this enables us a considerable amount of flexibility not just for how we look at things organized today, but how we may look for things

Page 177

that are organized when we discover mechanisms that we don't know about today -- when we discover new treatments that we don't have a lock on today. These ontologies have shown themselves to be incredibly robust about adapting to those future cases.

So how do we actually do this? And I think this is a really fun way of looking at it because it speaks to the quantitative parts of our mind. By the way, the mathematicians and engineers we work with, they love to look at pain research because they can't find really a messier problem that is less deterministic than pain.

You know, they talk about airflow over a wing. Well, there are physics to describe that. And heart rate and blood pressure interactions, they're pretty good physical models. When we talk about pain, all bets are off. It's really a very rich collaboration, but they still want to organize it, and I don't blame them.

So there is actually an entire international standard for how we organize information. It's

Page 178

called the Unified Markup Language, or the UML. And the schema simply denotes what that looks like, what does that roadmap look like.

So three different domains. First, we were kind of defining an acute pain taxonomy or ontology if we link this up further. We'd eventually like to disseminate this, and this is what Mike is going to be working on this afternoon to get it in print tomorrow. And then we'd eventually like to operationalize this to use in research in clinical and other domains, public policy, education, et cetera.

What does our timeline look like? Well, we're doing this today and tomorrow, and Mike's going to disseminate this tomorrow. But this is going to go on and on and on, and we're going to have to -- this is going to be repeated, to some extent, but we're always going to need to use this ontology.

This is not a one day event. It's not going to be a recurring one day event. What we do today makes a difference for a very long time. And we

Page 179

actualize this good, very rich discussion. We'll disseminate this for a publication and other output venues. But really, the operationalized systems, at least in this generation, it's through the electronic medical record systems because then it's in the United States being the common interacting footprint, and we need really big data sets.

In one of our recent experiments, we were looking at 144 different types of states for a given pain intensity rating in terms of how they transition. And one of our researchers said, "I'd like to consider just one more step in the sequence." And we went from 144 different states to 20,500 different states with just one more consideration. And if we went up to two considerations, we'd be well over a million.

So we're going to need, at some point, to start looking at how we can unify this across the country, hopefully across the world. And that's going to be very dependent upon having an accurate ontology, so that when I talk about post-operative total knee arthroplasty pain, I know that somebody

Page 180

else is talking about the exact same concept in the exact same context.

There are established components of an ontology that are pretty well typified no matter what the domain is. Our domain is in pain, but if you were talking about airplane parts, we'd have a similar ontology, or a similar description of components, and the first is the classes.

So this is the general category. In general, as we'll get to later, we might think of chronic pain as a class, and acute pain as a broad class. The objects are those individual instances. So if I talked about a class of cars, an individual instance might be a Porsche 911, which seems like it would be a lot of fun to drive. If we looked at attributes, those are the descriptors of that object.

So how do I differentiate a Volkswagen Beetle from a minivan made by Toyota? Well, there are lots of different characteristics, and those are the attributes of those. And we saw in the prior example that we were looking at not just the

Page 181

value, but also the sites and the types and such.
One of the concepts I haven't heard mentioned yet, but I think is a really exciting opportunity, is this consideration of the methods component, and these are things we can do to the construct. I can diagnose pain. I can treat pain. I can risk stratify pain. I can look at pain outcomes. These are things that I can actually act upon the object in question.
So with the blood pressure, I can decrease it. With a car, I can drive it and steer it. But we now have a formal mechanism of organizing the methods, the things we can act upon for that construct, and look at organizing that as well.
The key, though, at the end of the day is the relationship. And it's not just the one-to-one vertical tree-like structure, but this can be very intricate in networks horizontally as well. A lot of times, we actualize this by looking at the verbiage, so we see blood pressure is a vital sign. It has a site. It interacts with. Those are the key buzz words that are denoting the interaction.

Page 182

So in your discourse and discussions, if you realize that using the frame, acute pain has a mechanism, oh, well we have a relationship there, and it's worth mapping this out as we move forward.
So we'll go over some of these broader constructs. The first is the notation for the schema of classes, simply usually a box, and we have a vehicle. We can actually put specific instances of that vehicle, usually after a colon, or sometimes as a separate line.
Keep in mind, though, that we can have lots of different cars, and so in some cases, this ends up being very -- we call them super classes or subclasses. So just because I have an object in this car, I can also redefine car as another type of subclass, and we can go on and on. We'll get later into some discussions about where we draw the line and say, no, this is too much splitting or too much aggregation.
The Unified Markup Language organization is very neat, at least according to our engineering colleagues. We have the object name or the class,

Page 183

in this case up here, which is a car. We have the attributes listed here. Then we have the things we can do, or the methods listed below. So it's a nice organizational approach to mapping out these concepts. We can have a class, and again, it denotes a specific object. Notice the organization is very similar, but we have specific instances or vocabularies.
Earlier, we had talked about whether there was a given vocabulary or listing of terms that would fully describe and attribute, and this in that case would be let's look at all the different colors we could paint a car, or all the different engines we could put in a car. And at some point, then you have a menu item of things.
That helps a whole lot when we're starting to trade information and make sure that all of our schemas agree with one another, that when I say I have a silver car, I also know that you have a silver car when you say silver, and we're not talking about charcoal grey versus black.
The attributes can also take a slightly

Page 184

different variance here. We can talk about intrinsic properties of the object, and this is more of the philosophical discussion. Those are the physically imbued objects -- or physically imbued properties that are characteristic of that object. There's generally not debate about what we see there. Then there are the extrinsic, the ones that depend on external relationships, prior perspectives, a little bit of opinion, et cetera, et cetera.
Very importantly, just as we talked about how objects sometimes need to be reconsidered as classes, sometimes attributes can be classes onto themselves. Confusing, but allows us to further characterize what an engine is.
I probably don't need a whole lot of characterizations about color, but I may want to look at a 4 cylinder versus 6 cylinder engine for instance. And I'm going back to the engineering example here because this is concrete. There's not a lot of debate. I think a lot of us have exposures and experience with motor vehicles, so we

Page 185

can put this into a little different context. We'll come back to map it to pain in a little while.

The relationships end up being the last component, probably the most important. And if I had a question of like what was your trip like, I can look at different domains, the food, the people, the hotel, and notice with the vehicles I can talk about the different kinds of transportation you used during that trip. But I can also get circular. I can offer a class or a construct such as parking that ties maybe what the parking was like at the hotel, but also what that vehicle was like.

So I'm not going to offer any specifics here, but this is a framework for when we're discussing about acute pain and we have things start crossing into different domains and overlapping, we now have a way of visualizing this, and at least reliably reporting it from one party to another, so that we can at least agree what we're trying to say. And whether that's the right

Page 186

thing or wrong thing, that's a different discussion, but hey, we have a tool in the toolbox now.

When we developed this schema, we also have a concept called "inheritance." And what this means is that each of the attributes share something in similar to the class above it. So if I have a class of cars, that's a subclass of vehicles. We can begin to see that these take some of the characteristics of its parent class.

Now strictly, it's supposed to subsume all of the characteristics of its parent class, and then offer some additional ones. But there's lots of ample opportunities for this to be violated in practice.

So what we see, again, looking at our relationships is that a bike is a vehicle. A car is a vehicle, and a plane is a vehicle, too. We have a parent or super class. We use these terms interchangeably, and children are subclasses. We have more general as we go up, and more specific. We generally try not to get more general as we go

Page 187

down. We need to reorganize that if that's the case.

Very importantly though, we say, gee, this plane is just a different kind of vehicle, right? There's a lot of -- I mean, cars and bikes generally don't have wings. They generally don't climb, or at least into the air. And so we may have to put in an intervening super class here so that we can further differentiate planes into helicopters, airplanes, jetliners, rockets, what have you.

It's an organizational approach, but in doing so, each of those subtypes of planes will still carry the key characteristics of the vehicle as we defined it. Again, it allows us that vertical structure so that we can relate complex relationships to keep the similar things kind of similar, but still niche out so that we can take care of the exceptions where they may be.

So how do you know how many classes and subclasses to do? For instance, one of the worries you have is that you could create a taxonomy that

Page 188

has a heading of chronic pain, and then 10,000 different types of chronic pain, each of them incredibly narrowly specified.

Actually, that's quite elegant in many domains, but it becomes very problematic if I try to start lumping them together, such as I'd like to look at all the patients with a headache. Okay, there are a lot of reasons to say that headache's not a good grouping example, but I may have a reason to differentiate that from toe pain for some research or clinical question.

So having a very flat horizontal structure becomes problematic because I don't have a mechanism where I can reliably cluster things together with any measure of organization.

Some folks from Stanford suggested that we should consider the 1 in 12 rule, where if you have an organizational structure where one parent has just one child, this child probably needs to be rolled up into the parent. But likewise, if we have more than 12 subclasses of a parent, we probably need to put in some intervening groups up

Page 189

here. They don't need to be perfect. And again, they can still cross laterally. But it begins to suggest that when you organize this, it becomes a little more human, human machine interpretable.

Another fascinating thing I think that was brought up in the discussions this morning is just what do you do when you have multiple inheritance patterns? And we'll steer away from pain, and we'll go to something a little simpler, wine, and we'll say what if we have port wine?

Well, you could easily classify that as a red wine. It is indeed the color red. But it's commonly not a dinner wine, I am told. It's usually used as a dessert wine. So where does it fall?

So you could create a separate category, but in an ontology, you just say, you know what, it's got attributes of both. The types of attributes it has are similar. We can talk about the color. We can talk about the taste. We can talk about the typical volume. And while those values will be different, the attributes used to describe them,

Page 190

the categories of information used to describe them are similar, whether we're looking at either of those two parents. So this allows us again a lot more flexibility in how we consider these concepts.

How do we know when we're thinking about a new domain of knowledge whether we should consider this a class or a concept under this framework? Well, Noy Mcguinness, again from Stanford, came up with a very nice example. I won't read it to you, but it gives an idea of whether we consider this as a restriction, in other words does it disallow certain other categorizations, or is it just another characteristic that's going to be more universally shared. And that can help us distinguish between the two.

Another perspective on how you make this decision is looking at how you would organize in classes here. And again, we'll have all these slides available to look at this in further detail.

This allows us to move to the top down, bottom up approach. Now that we have that vertical structure in mind, we can start with the general

Page 191

concept, broad classes, acute pain versus chronic pain, toe pain versus headache. And do we work down to is TPRV1 versus 2 presence in each of those, and that's the top-down approach. Or we can start with pure mechanisms, or treatments, or method, or any other methodologies we'd like to look like, and then try and aggregate in kind of a bottom-up approach, if you will.

Why are we doing this again? Well, it allows us to independently decompose each characteristic. So we can say, well let's look at classes and then specific instances of acute pain for instance here, post-operative, amputation, central traumatic, cancer. And we can separate out the attributes, or I think the dimensions did a very nice job of aggregating many of the common attributes that we may want to flesh out in this. But we also now have this new concept of methods when we say what can we do to that pain.

So as we think of new terms, we can start by saying, how would we put those terms into this general framework.

Page 192

Very interestingly, there's a five-step program for lots of things, that includes making an ontology. And the first test, as the good Dr. Mackay pointed out that's a preamble to this, is try and borrow from somebody else first. That may not be available and commonly isn't, but it's still worth looking.

I will say that my interpretation so far of ICD-10 and SNOMED CT, it does some of what we would like, but not quite there. But very importantly, everything we do for the rest of these five steps will probably have to be remapped in some variety back to those other sources so that we can have some type of common language when we're discussing these concepts.

After you determine the domain and scope of what we'd like to talk about, so we're going to talk about acute pain today, and we're not going to talk about the environment. We're not going to talk about political landscapes. We've defined our domain and scope to some extent.

Then we list in a brainstorming session the

Page 193

terms for consideration. And a lot of this has already been done it sounds like in the first meeting, where we then looked at different classes and hierarchies, but more importantly attributes as well.

So those terms, if you will, would be what we'd flesh out into here. And we just have a broad vocabulary of terms, and we'd start slotting them in, whether they're classes, attributes, methods, et cetera. And there's a lot of discussion, I'm certain, to be had in that framework.

Then you start creating specific objects, specific instances, and I think of these as those exemplars that were discussed earlier this morning. We're going to talk about certain subtypes of pain that are universally agreed clusters, if you will, that we kind of look at and say, yeah, I'll agree that there is a subtype of acute pain that may be associated with post-amputation pain. But those are specific objects that are going to carry their own set of characteristics and will probably be hierarchically related in some variety to other

Page 194

concepts, even if they're just considered a subtype of acute pain.

So what does that mean for us today? Well, if we look at our 5 dimensions that were discussed elegantly earlier in our talk, we see that there are very much attributes. We can look at the core diagnostic criteria of a type of acute pain, the features of that pain, the medical comorbidities, consequences, risks, and protective factors.

We could offer the opportunity to include additional dimensions or attributes such as the temporal nature. You could consider listing the response to treatment, or you could consider that just as a method. But these are the different ways we can characterize those concepts, if you will.

So we'll kind of zoom in here. These are our attributes. And the attributes are then kind of put out there as the terms we'd like, and then we'll talk about the classes. We talked about those exemplar papers here. And there's already been some discussion of subclasses of acute pain that will be the topic of many excellent talks

Page 195

tomorrow throughout the day. And those are basically soft entries into what we'll see here -- in just a second, I'm sorry -- the objects.

I think it is worth discussing whether we should include the methods earlier. Entire lead up discussions to this meeting, there had been some talk about, well, gee, should we have quantitative sensory testing characteristics then as an attribute? Could we look at imaging results, for better and for worse, and their specificity and sensitivity as attributes, or should we consider those as a holdout category of things that we can do on these pain concepts?

They're methods. They're things we can do for a patient presenting with a specific type of pain, or not to. It's okay to keep some of these empty.

Very importantly, each of these can be lumped and further cut into a separate series of classes onto themselves. So for instance, we may have several different imaging modalities that we may want to separate. We may want to have entire

Page 196

separate classes of mechanisms for comorbidities. For instance, we may look at psychiatric comorbidities and differentiate those from medical and surgical comorbidities.

At the end of the day, this is what we're trying to get to, I believe, in terms of looking at some generally agreed upon subtypes of pain that are going to be comprised of attributes and potentially methods that are used to characterize these objects. And these objects will fall into some organizational structure under these classes.

It may be one layer, as has been known so far with chronic pain. We may find that certain types of objects share a large number of the attribute details, such as mechanisms, the expected comorbidities, perhaps response to treatment, and that may serve as an opportunity to develop subclasses for further organization.

So again, let's look back. We have determined the domain and scope. We can list important terms for those consideration. We've defined classes and hierarchies for consideration.

Page 197

We may want to start lumping things together in 5 here based on the attributes we have for those classes; again, a kind of overall schema of how this would look like in a UML interface that would be more applicable to electronic medical record system or any database used to flesh out patient specific details for where they fall under these domains.

So now we can look at a couple of examples. Let's say we have acute pain and we've decided there's going to be a post-operative pain. We'll have 5 different attributes, or maybe mechanisms. And each of these diagnostic criteria may be a very long list of things that could fulfill it. It could be a dropdown menu. It could be values we enter as integers.

We may do certain diagnostic tests to see if it's post-operative pain. I'm not sure what those would be, but you could. You could also say what treatments this is most likely to respond to. That may help us further segment these types of pain.

Again, we're going to organize it as super

Page 198

class and subclasses, the attributes and the methods. We begin to see, well, here are a couple different other subclasses of acute pain that we can look at, and now we get into yet another layer. So we've agreed that there is -- let's just pretend that we've agreed that there's a post-operative pain class based on the acute pain super class.

Well, let's call this alpha and beta. Maybe this is thoracotomy and knee replacement. We see that the attributes or dimensions are similar, but the values used to fit in are different. The values here can help us inform how to organize these. We may be able to do that empirically, or we may have to do this quite analytically.

Interestingly, the analytical approach is very automatable and naturally updateable and can allow us some objectivity in how we cluster these things together, provided that we have an agreed upon vocabulary or list of possible variables that can be used to specify each of these attributes.

Another interesting detail is that despite having two different types of post-operative pain,

Page 199

we can then further subdivide the treatments, these methods, into their own sets of classes. So this can become a little bit recursive, which is a little confusing, but it also allows us considerable flexibility so that we don't have to know about all the treatments today. We just know how we would characterize the treatments.

I don't have to know about all the different types of post-operative pain today, or even all the other subtypes of acute pain today. I just need to know how we would characterize them, and that it's okay to interrelate them to other disciplines as we move forward.

Again objects, and here we have methods as classes. We're allowed non-linear relationships, so that we can give ourselves considerable flexibility and allow us for overlapping.

I want to make sure I'm very clear on this point. I am not suggesting that this is a wonderful idea or the solution to all of our ills. This may actually lead to a much messier definition than we would like. But I think it's very

Page 200

important to recognize that the capability exists and would fit in very well with other ontologic structures used in other healthcare domains for folks trying to link very difficult concepts where they say, well, this is what we see and this is what we're able to measure, but there's this underlying truth of probably a lot more complicated.

These non-linear confusing relationships are an intervening step that allows us to take our current concept map and still link it to some future, better but unknown concept map that's hopefully coming tomorrow or next decade.

So we've gone over the need for ontologies. They're very important. This is how the United States is rolling out its electronic medical record system. At the end of the day, it's all about where your data objects live and what they actually mean when we talk about a blood pressure or an acute pain episode.

The schema architectures I think are a nice way for us to codify this as we have discussions or

Page 201

you're trying to get somebody else to say, oh, this is what I mean, or this is how I would organize this. I think it's a very nice, universally accepted method that you can take to your hospital folks, to your IT vendors, and say, look, this is what we want to do. And instead of it being a two-year project, hopefully it's something a little more expedited because you've already taken the initial intake steps.

We can readily apply this to the work that's already been done. The concept mappings I think are very clean. The dimension structure fits into the attribute structure very well.

So even if we don't use any of the schema, I think it's very important to take at least this terminology back to your home institutions and say this is what we'd like to do based upon what we've agreed upon and this action team. Can you help us with this? And they'll recognize that, hopefully, and say yes. And we're four steps down the road rather than having to try and figure out what each other means.

Page 202

So thank you all very, very much for your time. Appreciate it.

(Applause.)

DR. CARR: Thank you very much, Patrick.

So as we alluded to earlier, we will be having a panel on the discussion of how or if the AAPT dimensions should be modified, but in order to continue to give and provide more thought and context to support that later introduction, we've moved up Steve Bruehl's talk from tomorrow afternoon to today.

Steve played an integral role in CRPS and in the whole scientific leadership of formation in an evidence-based fashion of the AAPT dimensions. Steve is a professor of anesthesiology at Vanderbilt, and I'll turn the podium over to Steve.

Presentation – Stephen Bruehl

DR. BRUEHL: Thank you. Patrick, that was excellent. I now understand on a much higher level what we did with AAPT.

(Laughter.)

DR. BRUEHL: I guess we didn't do too badly.

Page 203

All right. So the reason I was moved up is we were realizing, as we were listening to some of the questions this morning and kind of what are task is here today, that going over some specific examples of Dimension 1 and the issues involved in that might actually help focus our attention in a more productive way.

Because as you can see already, there are all these different directions we can go of on. And at the end of the day here, we want to have a plan for how to proceed with something that is tangible and useable. And what I'm going to do is talk about the Dimension 1 only, okay, not to say that it's more important, but this is something where we can actually validate what we're doing, whatever we come up with, and I want to show how you go about validating it.

I was telling somebody at lunch -- and you will see in a sense that the emperor has no clothes, and I will admit that right off there -- just by the nature of what we're trying to do, there are inherent problems in doing that and

Page 204

trying to take an empirical approach to proving that we're doing something right. But I will explain some of those ins and outs, and hopefully that will help.

I think based on what Dan mentioned earlier, this is all about constructing reality. We are going to define what X condition is. That's our job, and we have to do it as well as we can. But that's really what we're trying to do is define these conditions. Nobody else is doing this, or they're not doing it the same way we are doing it.

According to what Patrick just said, I think what we're going to be talking about here primarily are the attributes, which would be the diagnostic signs and symptoms that go with the objects, which in this case would be a particular category of chronic pain, is what I'm talking about here.

So, two issues to be considered. These are just the conceptual issues here. One is validity, and this is simple question, are we measuring what we think we're measuring. The other one is reliability. Can we measure the same thing over

Page 205

and over again and get essentially the same result, either over time or across individuals?

Now, while these are independent constructs, they do interact somewhat because you can't have a valid diagnostic category that is not also reliable. You have to have reliability for it to be valid.

However, you could have an extremely reliable set of diagnostic criteria that are totally meaningless because they are not in any way reflective of the way reality is. So we have to keep in mind we need to in an ideal world demonstrate both of these.

Now, I'm going to start out talking a little bit about reliability. There are a couple of different types that we're concerned with here. One is interrater reliability. And this is if we have the same patient seen by two different physicians, would they both come up with the same yes or no response to individual criteria within our set of diagnostic criteria. And the second related question is, would they come up with the

Page 206

same categorical yes/no answer as to does this particular patient have this disorder. It's just a dichotomous decision.

So it's kind of two levels of interrater reliability. And then we've also got test/retest reliability, and this just means over time, if we were to make the diagnosis over a period of several days, would this end up with the same result each time. And would that dichotomous decision end up being the same on each of those instances.

This can either be within one diagnostician, and that would be what's sometimes referred to as intrarater reliability. Or this could also be across multiple clinicians.

This would be the situation where you've got somebody comes into my clinic for a specialty evaluation. I do it. I say you've got X disorder. I send them back to the referring physician, and the referring physician now is thinking, all right, they say you have this disorder, now I'm going to evaluate this, will I come up with the same decision. So when you've got referrals, this is

Page 207

actually a real issue.

One aspect that's really important -- and this ultimately comes down to wording. And I love the people I've worked with on AAPT, but I have to say that there have been varying levels of appreciation for the importance of how things are worded. Tiny wording changes can totally alter the intent of things. They can totally change whether they can be operationalized or not.

There are a couple of examples here, and this is a real example from the IASP criteria for CRPS. This was from the 1994 criteria. It said, "Evidence of changes in skin blood flow."

Now, in one sense, that seems very clear what that means, but when we say this person has to be assessed, what does that really mean? Do I have to get a Doppler, laser Doppler measurement to be able to decide that? Is that something where I can just look at the color of the skin? Do I need to use an actual thermogram to quantify digital temperature really finely? If so, over what area?

So there are all these layers of issues,

Page 208

kind of like the definitional issues that Patrick was talking about a minute ago with blood pressure. So ideally, we want to specify as clearly as possible how you would assess these things.

Another hypothetical example, if we just say progressive distal sensory abnormalities, well, that's great except what are you including in that? Positive signs? What about negative signs? Would you treat those the same way? Would pain related abnormalities be considered part of the sensory abnormalities, or is that separate?

So how those are worded is going to have a big influence on whether two people could agree that that sign is present. So the wording is important.

Also, let's say in a set of criteria we've got four different specific criteria, and in some cases it may be you have to have all of these to get the diagnosis, but frequently there's kind of a Chinese menu approach. You have to have at least 3 of these 5, or 3 of these 4,k or whatever it may be. Those are called decision rules. It's how you

Page 209

come to that dichotomous decision as to whether a person has or meets the diagnostic criteria.

Now, obviously, if you have a rule that says 3 of 5 criteria have to be met, that's very straightforward. It would be easy to have two individuals agree on that. But in some cases -- and I've actually seen some instances like this in the older psychiatric manuals where there are very complicated decision rules.

So you have to have criterion A. We've got a list of five things for criterion B. You have to have at least two of those. And criterion C, you only have to have if you have less than 4 symptoms in B, which makes you think a lot. And the more complicated you get in those decision rules, the less likely it is that two people are going to agree that a given patient has the diagnosis. So wording matters.

When we're talking about test/retest reliability, we do have to consider the context of the situation and would clinical features or those diagnostic decisions be expected to be stable over

Page 210

whatever time period we're assessing them over.

Now, with acute pain, if we're comparing day 7 to day 21 post-op, in many cases, we would expect that there would be pretty dramatic changes in those features over that period of time. So in that context, test/retest reliability may not be very meaningful. But if we're talking about two evaluations in a given day or from day 1 to day 2, we'd expect a fair level of consistency there.

I think the main thing to remember here is criteria that can't lead to people making the same diagnostic decision, both within a person over time and between providers, really is not going to be of very much use clinically if it can't do that over brief periods of time get those same decisions.

So you can test this. There are different ways of doing this, and these can either be focused on the individual criteria themselves that we're trying to operationalize, or it could be focused on the overall diagnostic decisions.

One way of doing this simply and cheaply are vignette studies. So an example of this might be,

Page 211

we would do a videotape of an actual patient being examined, where it's done in a way where you could actually see exactly what the clinician is looking at. You can hear all the questions being asked. You can hear the responses.

So we've got a standardized evaluation, and now what we do is we hand clinicians our diagnostic criteria and say, use these criteria based on the information provided here on this video to tell me whether this patient has X disorder. And you get multiple people to do that. And that is one simple and cheap way of finding out whether you have reliability in those diagnostic decisions, or even in those individual diagnostic criteria.

Now, the problem with that is that it doesn't necessarily generalize well to real-world clinic settings where you can interact with the patient, get more information, redirect things. So it has some utility, but I wouldn't want to rely solely on that if I had the resources to do something more than that.

But I think vignette studies could be useful

Page 212

for fine tuning wording before you do the expensive studies, which we would call a field trial. And this is where you've actually got real clinicians with real patients sequentially doing evaluations of the same patient, ideally over a couple of days, so you can get at this both within individual and between individual reliability issues.

So these are very doable studies. They can be done on any particular condition. All you've got to have to do this is some money, some clinicians to do the evaluations, and you have to have a draft set of criteria, or what is most likely to be happen is we're going to have our AAAPT-1, which are the consensus based/literature based criteria. That would be what we would test with this. And we might discover that some particular aspect of this condition, the way we've worded it is very unreliable.

Well, that tells us we need to alter those criteria, improve them to address that problem. And then if we do that with the vignette study, now we can test it in the field trial and see if it

Page 213

works very well.
So not to bore you with statistics, but I do want to mention a couple of things. And I have to say, I saw this large -- it's in Europe. But it's a government-funded study, huge study, and they published this thing on test/retest reliability, and they were reporting correlations.
That is a huge no-no because correlations do not factor in that you're going to get agreement by chance to a certain degree. So what we want to use is something called kappa, which is kind of like a correlation for dichotomous variables that would factor in chance agreement. You're going to get an inflated value if you're looking at correlations.
There's also something called the intraclass correlation coefficient, which mathematically is interrelated with kappa, but it can handle the ordinal, interval, and ratio variables. They all are kind of ranged just like a correlation would between zero and 1, and higher is greater reliability. And the gold standard in the literature seems to be somewhere around 0.6 or

Page 214

higher is acceptable. Obviously, the higher it is, the better.
Now, I want to move on to talking a little bit about validity. This is where the hard part of this whole project comes in. So our question is, do the criteria we come up with reflect what they are supposed to reflect? So if we are targeting X condition, whatever that is, do the criteria we come up with accurately reflect that condition?
Conceptual issue, and I hate even having to talk about this because it makes my head hurt. So what is X pain syndrome? What defines what that is? Take a step back from the way you normally practice because you probably apply labels all the time without really thinking always how you get to that decision. But step back.
Where did you get the idea that these particular features are what indicates a patient has X? And what is that actually based on? Was there anybody that ever proved that that was the case? Was this your training? Was this some consensus you've seen in the literature? So what

Page 215

is the origin of that?
Who defines it? Are we taking something that came up with a consensus group that you read somewhere and that's how you've defined it? It may be perfectly acceptable to do that, I'm just saying to think about, as you're creating these, where you're getting the information you're basing those diagnostic criteria on.
How do we measure that syndrome? How do we measure the components, the clinical features of that syndrome? Sadly, in many cases, and I'm sure this doesn't apply to any of you, but there's a situation where you will literally get the response, "Well, I know it when I see it." Based on what? "I just know what it looks like."
So it's like a gestalt. Maybe a little hard to pin down exactly what they're looking at, although I think that any clinician who says that, you could probably work with them to put on paper exactly what that means.
Finally, if you come up with this definition that defines X disorder, will everyone agree on

Page 216

this? Well, they probably won't because, as I said at the beginning of this, we are constructing reality and people have different realities. They may not like what we come up with, but we have to do something.
Now, the problems are that pain is inherently subjective. Maybe Sean's imaging research suggests there are some ways of objectifying pain, but in normal circumstances we're not going to have a means of doing that very well. And because it is subjective and because we don't know pathophysiology very well for most of these conditions, we don't really have a gold standard to use as our reference point for saying that this set of criteria is good and this set is bad. There is nothing independent of the subjective pain itself.
I also have here noted this in quotes here, "fuzzy boundaries." That's kind of my way of thinking about what Patrick was talking about a minute ago about the different classes, and how closely or how far apart they are. Because you may

Page 217

have classes that literally overlap. They share so many common features that if you were to map it out, it would look like they really are not very distinct. In this context we're talking about certain chronic pain conditions.

An example I was actually involved in years ago was migraine headache versus tension type headache. Are they really two different types of headaches? They overlap clearly a little bit. They both involve head pain and may even share some other characteristics in common, but are they really different?

In some sense, in an effort like we're doing here, what we're doing is we are arbitrarily saying here's the dividing line between this condition and that condition, and we're going to write our criteria to make sure that there is a clear dividing line. Now the reality underlying that may be that those conditions do in fact overlap, but that's something that we can actually test in certain types of research we might do.

So because of the subjectivity and lack of a

Page 218

gold standard, any pain syndrome, whether it's acute or chronic, is really at best going to be a syndrome that is a construct, which we are assuming exists. We have created something that we hope reflects an underlying construct. And you cannot show absolute validity for these constructs. The best we're going to be able to get is relative validity, relative to some reference standard we pick.

There are several types of construct validity that may be relevant; content validity, that is are we actually doing a good job capturing whatever the domain is that should be reflected by that condition.

Now, this is the one place where patient input may be particularly valuable because they may be able to help inform what types of things they consider important in somebody who has this type of condition. So it's like are we measuring adequately that whole domain that we're interested in.

Internal validity, I'm not using in the

Page 219

sense that statistical design people would talk about it. I'm talking about the validity of the internal structure of the criteria. So if we've got a diagnostic category and we have 4 different diagnostic criteria within that, are the way that the signs and symptoms are broken out across those 4 criteria valid? Do those subgroupings make sense? And I'll give you an example later of exactly why that issue is important in a pragmatic situation.

Concurrent validity. So we pick a gold standard. We don't have an absolute gold standard, but we can pick something that is our surrogate for that, and we can see do our criteria match up well with that.

Convergent validity, I remember this phrase from graduate school. I always liked it. The nomological net. It sounds so mysterious. And what it's talking about is we have this construct we can't really measure that's floating in space here, and around it we have all these things we can measure, and we have expected associations between

Page 220

those measurables and what that underlying construct is.

So the specific example that I would give of this is in the ACR fibromyalgia criteria, they don't explicitly talk about doing quantitative sensory testing to look at degree of temporal summation, which is an index of central sensitization.

Now, theoretically we would expect fibromyalgia to have a lot of central sensitization, and we could measure this, but it's not part of the diagnostic criteria. So that would be an example of convergent validity, somebody who's showing a high level of temporal summation and getting the fibromyalgia diagnosis.

Finally, we've got discriminant validity, and this is when we have two -- in this case, let's say we're talking about two different acute pain conditions, and we've got diagnostic criteria for each. The question is, can we reliably distinguish between those two conditions? And if we can't, then we've got a real problem because it would

Page 221

suggest that maybe the objects in our class are not two objects but rather a single object.

So if we have to pick a gold standard, what do we use? If you go look at the literature on people who have tried to validate diagnostic criteria previously, they're really a pretty limited number of features.

Now, pain is not like something like Alzheimer's disease where you can do an autopsy and look at the plaques, and look at their clinical signs and symptoms before they died, and make a direct association.

We have these, what I call sometimes the bronze standard, or tin standard, or something a lot less valuable than gold, but it's all we've got. Now, we might use whatever the current consensus based diagnostic criteria are.

So when we developed the CRPS criteria that were adopted by the IASP in 2012, what we used were the consensus based 1994 criteria. We also could use just this fairly vague term of usual method of diagnosis.

Page 222

Now, as loose as that sounds, that was actually the gold standard for validating the fibromyalgia criteria that are used even today. It's a pretty poor gold standard, but really it was all we had at the time to do that.

We've also got expert clinician diagnosis, which is probably not really much different than usual method of diagnosis honestly. That's what they used doing the DSM for psychiatric disorders in the version 3R. And then they can use previously published diagnostic criteria, so DSM-4, DSM-5 were evolutions based on the previous version. That was the gold standard they used. So we do have some gold standards we can use for research.

Now, if we're trying to do empirical validation, there are some statistical pattern recognition techniques that may be useful when applied in certain ways. And these would include things like principle components analysis, which is similar to factor analysis, cluster analysis, latent class analysis, and classification and

Page 223

regression tree models.

Some questions that we might address, some things we might do using those types of techniques, one would be to identify groups of statistically similar patients based on patterns of clinical features. So let's say that we are interested in --

Somebody throw out an example. What's a pain condition, an acute pain condition you'd be interested in? What? Fracture pain? Okay.

So you've got fracture pain and we get multi sites, and we see fracture patients, and we start systematically collecting data on the types of symptoms they report, the objective signs that they exhibit when you examine them, maybe in this case x-ray results or other kinds of objective testing like that. And what we do is we have then this big database of features that might be associated with fracture pain.

Now, what we're interested in is what is the core of this. Is there something we can narrow this down to, a set of core features that are

Page 224

prototypic? So now what we do is we use one of these techniques like the principle components analysis, and you can even use cluster analysis for this, to try to narrow that down.

What you'll see is, it will tell you which of those large set of features you're looking at hang together. Which things tend to covary? Because when they covary, that suggests that there is some underlying construct that it reflects, and that's really what we're interested in, is that underlying construct.

So we could use that type of approach to narrow down our domain from something really broad to something that may be more clinically practical and narrow that really represents the core of whatever that pain condition is.

Now, we also could identify groups of signs and symptoms that cluster together within a given patient population, and this is for the individual criteria.

So in this case, rather than looking just at throwing a whole bunch of features into an analysis

Page 225

and seeing what comes up, we have more -- we may have a draft set of criteria for example that have certain signs and symptoms split out a certain way, and we can use these types of pattern recognition approaches to determine whether that way we've broken it out is actually supported by the way the data appear in a real-world data set. Because if what we have in our criteria match up with the way things really are in the real world, then we've done a good job of reflecting that.

Finally, we want to show in some cases, and this is the fuzzy boundaries issue, are two conditions distinct? So we literally use cluster analysis on a large sample of migraine and tension type patients, and it was very simple.

We told the program -- we said, give us a two cluster solution based on the signs and symptoms we did. And then through everybody else, we have a group the computer says is one type and another type, and we've said, okay, how many in each group actually got a diagnosis of migraine versus tension type? And sure enough, it's about

Page 226

90 percent accurate in both groups.

So it really supported the idea that these are different statistically distinct subtypes of headache. You can do that with any two conditions. It's particularly useful, though, when you've got conditions that you wonder whether they may overlap.

Common validation questions. Do the criteria that we've proposed have concurrent validity relative to some existing reference standard? So this might be whatever the field considers the best set of consensus criteria. It may be some professional organization's criteria that's listed on their website. It could be anything you pick.

The other question is, do revised criteria improve discriminative validity relative to existing criteria? So you'll notice on that second question you don't have to know absolute validity. All we're trying to say is when we change things, can we do a better job than we did before in discriminating two groups?

Page 227

How would we do this? If we're looking at categories of things, how do we know we've done a good job? Well, you've got the obvious thing of overall accuracy. It's a simple number or percentage. It really is not very informative because nothing is ever 100 percent accurate. And when it is not 100 percent accurate, it's really good to know why it was inaccurate. Was it false positives? Was it false negatives? What was the proportion of those?

So what we're really interested in primarily are sensitivity and specificity. Sensitivity is the true positive rate. Specificity is the true negative rate. So true positives would be that they actually have the condition that we're interested in studying, and true negative is somebody who clearly does not have that condition and are we accurate in making that judgment.

Positive and negative predictive power, these are actually the probability that if I make a diagnosis that somebody has the condition or doesn't have the condition, the probability that

Page 228

that is going to be accurate.

The problem with that, while it's a nice idea, is it's dependent on the base rate of the disorder in the population, and frequently we don't know that very accurately. So it's subject to a lot of swings in magnitude depending on what assumptions you make.

However, there's another option called positive and negative likelihood ratio that can be directly calculated from sensitivity and specificity that gives you a number that can be interpreted in a fairly similar way, so that's probably preferable.

So a couple of things to point out here. Now, sensitivity and specificity are interrelated. If you change the wording of your criteria, you change the decision rules, both are going to be affected, generally in opposite directions. So if I have a set of criteria that has 4 possible criteria that they could meet and we say as a decision rule, you have to have 2 of these 4 to get the diagnosis.

Page 229

How does that differ in sensitivity and specificity from if we say, you have to have 3 out of 4? What we can do, if we want to do it elegantly, is we can plot sensitivity versus the specificity on what's called a receiver operating characteristics curve, and it will allow you to find the cutpoint that will give you the optimal balance between sensitivity and specificity; somewhat arbitrary, because you have to decide what's more important.

In a clinical situation, generally, we are most concerned about not missing diagnoses, so we have to put a high priority on sensitivity. We don't want to over-diagnose people who don't have the condition, so we have some concern with specificity, but relatively it's probably a little lower than sensitivity.

In a research context, you might argue that specificity is a little more important because we really want to make sure that everybody we get into our research samples absolutely does not have other conditions, and there are ways of altering the

Page 230

decision rules to do that.

Have you ever heard where receiver operating characteristics came from? This is from World War II radio operators. It was something they come with then, which I didn't know for a long time.

I'm going to spend the rest of this talk on the very specific example of complex regional pain syndrome, showing how we use the approach I just told you about to modify criteria in a way that we hope has improved them.

Now, truth be told, we did not do reliability testing. This was totally unfunded effort, just did not have the resources to do it. We were depending on the good graces of the people that were collecting data for us. So we were able to look at some of these relative validity issues but not really the reliability issues.

So we started with just a rational approach looking at the criteria that had been published by Merskey and Bogduk in 1994 in the IASP taxonomy that has already been discussed some today. That's when they were fighting, right?

Page 231

So criterion 1, presence of an initiating noxious event are cause for mobilization. It actually says in the footnote, you don't have to have this to get the condition. My question is, well why include it? It doesn't add anything to the diagnosis. I think that was a compromise I would guess.

Number 2, continuing pain, allodynia, or hyperalgesia, which is disproportionate. So any one of those is enough to get it. So in theory, you could have no allodynia or hyperalgesia and have some continuing pain that you judge is disproportionate, and that would meet that criterion.

Number 3, this is the one that's the biggest problem, evidence at some time. Now, when you say at some time, if we take that at face value, that means I don't have to see this when I examine you. You could just come in and tell me that your arm used to swell really badly, and you sometimes got a cold arm and then it turns warm for no reason. And I examine you and everything seems totally normal.

Page 232

That still meets that criterion.

The other thing is, it lumps together things that on the face of it are very different, edema, changes in skin blood flow, undefined how I should assess that, or abnormal sudomotor activity. Again, not defined how I should assess that, but it all has to be in the region of the pain, and then there's an exclusion criteria at the bottom.

So the question is, do the criteria adequately capture the core defining features of CRPS? Is the structure of the criteria optimal? That is those individual criteria like criterion 2 and 3. Are the layouts of the signs and symptoms reflective of what happens in the real world? Are the diagnostic decision rules good?

The reason we're concerned with these is because that will influence the sensitivity and specificity. And in this context, when we're talking about sensitivity, we're saying how well do the criteria identify the CRPS positive cases. Specificity is how accurate are we in identifying the non -- screening out the non-CRPS cases.

Page 233

For the content, the domain questions, we went to the literature, and you could very quickly see that there were several features in the diagnostic criteria I just showed you that do appear in the literature a lot: allodynia, hyperalgesia, skin temperature or color changes, sweating changes, and edema.

However, if you look at the literature, you will also see very frequently mentioned a bunch of other signs and symptoms that were not included in those criteria I showed you. So trophic changes to hair, nail, and skin, tremors, dystonia, and so on. The question is, were those criteria, as I showed you before, adequate, or were we missing key features of the disorder?

So what we did was a multi-site study. For rare conditions, in particular like this, you have to use multiple sites to do this. And I would anticipate anything we do in this effort would require multiple sites as well.

We ended up with 123 patients who all met those 1994 criteria for CRPS I showed you, and they

Page 234

all underwent a standardized evaluation of signs and symptoms related to CRPS using a structured database form. There was an instructional video that showed how to do the exam or the different aspects that were covered on there, as well as instructions for how to do the different components.

You can't read this, but this is just an example. For signs and symptoms, they were all coded, symptoms here, signs down here. Symptoms are all yes/no, signs all yes/no, but within each broad category, such as temperature asymmetry, you could specify cold, warm, or labile.

So it was just laid out like this in a very easy to use way. The reason we did the dichotomous choices was to enhance reliability because it's easier to make a yes/no distinction than it is to get agreement on fine gradations of something like that.

Internal validity. Does it make sense to include both objective signs and subjective symptoms in the criteria? The old criteria only

Page 235

required symptoms. Do they provide different information?

Well, what we saw with this just looking at simple frequencies was that there were some parallels. These are the signs here, symptoms on the right. And you can see in red are the things that were most frequent. So color changes were the most frequent sign and symptom; same for decreased range of motion. And then in blue, those that were the least common were nail and skin changes.

So the rank ordering was similar across signs and symptoms, but you'll notice the absolute numbers for signs are always quite a bit lower than what we got for symptoms. What we took from that was that signs and symptoms both are reflecting real phenomena, but some of those features of CRPS are labile, and they may not be showing it on the day of clinical exam. And that would account for it being more common as a symptom than a sign.

So our interpretation of this was that both provided meaningful information, but they weren't totally redundant.

Page 236

Is the grouping of signs and symptoms in each criterion supported by the data? Well, you look at number 3 again here, so the question is this evidence at some time for edema, skin blood flow changes, or sudomotor activity changes, is that too low a threshold to say that all you've got to do is have one of those? Is it too easy to get the diagnosis?

So we used principle components analysis to identify groups of signs and symptoms that seemed to have underlying common relationships. They covaried together. And what you'll see here is that we got 4 relatively independent factors when we examined those signs and symptoms that we collected.

We had one that we called the sensory factor. This was basically allodynia and hyperalgesia. This was very similar to what was in criterion 2 that I showed you. There was a vasomotor criterion.

This is a component of criterion 3, but it wasn't the whole thing because what actually

Page 237

happened was a little surprising, was that the sudomotor measures, the sweating changes and the edema were linked together, but they were separate from the vasomotor.

So really, criterion 3 in those criteria I showed you statistically broke out into two separate factors. And then we've got the motor/trophic issues. They lumped together, but they were separate from all the others. And this is not even assessed in those criteria. So that suggested there was a problem.

So our conclusions were that those IASP criteria from 1994 are not really internally valid, and that it's a real problem when we combine vasomotor, sudomotor, and edema all into one criterion because it can lead to over diagnosis by making it too easy to meet that threshold. And it suggested a revision was needed. And what we wanted to do was to revise based on the findings of these studies.

What you'll see is -- and this is overlapping study. It's not exactly the same

Page 238

patients, but it's a lot of the same ones; 117 patients meeting those diagnostic criteria, and then 43 patients who had non-CRPS neuropathic pain, judged to be non-CRPS based on expert clinician opinion. These were things like PHN or diabetic neuropathy, as well as other specific neuropathies where the cause was known and it didn't seem to be CRPS.

The idea was simply that if the CRPS criteria could not be used to discriminate between these two groups, they really were not going to be very useful. That was the basic idea of this, is that CRPS patients should look different than these other type of patients because they have a much stronger loading of autonomic features and some of these other things that you don't always see as prominently in other neuropathic pain symptoms.

So we got the same standardized measure of signs and symptoms. And what we ended up with was sensitivity was great, as you would expect because of the way we did the study, but specificity was not. It was only 0.36, meaning that the people who

Page 239

had non-CRPS looked very much like those 1994 diagnostic criteria, so they were very likely to be misdiagnosed. Now, because of that over-diagnosis, this number gives us a reason to say we need to revise things.

We just point out AAAPT, we could do exactly the same process. So we come up with our first version of the criteria here, then we start collecting data, and then we can play around with revisions to those criteria based on the problems we see. And then we can compare our new proposed criteria to the first version of the criteria to see if we're actually helping things or hurting things. So the process is very similar.

For the CRPS example, one change we thought of, just based on looking at the results of all this, was requiring the presence of objective signs was going to be useful because it really didn't make sense to allow patients to essentially diagnose themselves, because it was really -- they didn't have to have any clinical features when they came in, patients could just read on the Internet

Page 240

what CRPS was and come in and say I've got these things, and that's the diagnosis.

We also thought it was important to include motor/trophic changes because they weren't covered at all, but in the historical literature they were clearly considered part of the same syndrome. We wanted to break out vasomotor features from the edema, sudomotor features, so we have two separate criteria.

We proposed these, and then at a consensus meeting, we went over all the data, discussed it, made a few minor revisions, and decided to proceed with testing the revised criteria that we came up with.

They are called frequently the Budapest criteria. The clinical criteria are what you'd use in normal clinical circumstances. The first thing is continuing pain that's disproportionate to any inciting event. The key thing there is, it's insisting that the patient has to be painful, because you actually get people who look like they have CRPS who say it doesn't hurt, which does not

Page 241

seem to be the same thing. So that was included there for a reason.

Then we've got a symptom block, and in that symptom block we've got these 4 areas that came out from the principal components analysis. And what we said based on the findings of our study was that if you have 3 or more of those symptom areas, you've got the diagnosis. Well, take that back, you meet the symptom portion of the diagnosis.

Now, we say for signs, you got the same 4 categories: sensory vasomotor, sudomotor, edema, and motor/trophic. And for this, you have to have at least two of the categories positive on exam the day that they are seeing you.

We also decided for research purposes to make an explicit recommendation for an alternation to the decision rule if you're doing research studies and you want to narrow it even further to make sure you don't have any false positives. So what we did is it requires 3 or more sign categories, and that's to increase specificity.

What you can see here is -- and this is not

Page 242

the original data I showed you. This is a totally separate study. We replicated the effect we got before, which was that the IASP 1994 criteria are very sensitive but had poor specificity. The Budapest clinical criteria continued to be extremely sensitive but increased specificity quite a bit. And the research, as intended, we knew it would drop sensitivity but it did in fact increase specificity.

So this tells us that the new criteria are not perfect, but the numbers would say that they're better than what we had before. And keep in mind, this was all done in the absence of having any objective gold standard.

The IASP taxonomy committee finally agreed to adopt this in March of 2011, and it was adopted by the IASP board. It is now on their website. It's official. And now the clinical trials are using this as their diagnostic criteria because it is better than what was out there before. It kind of filled the gap.

Take-home point of all of this, if you

Page 243

remember one thing as you're trying to plan out your AAAPT criteria, the wording matters, and it matters a lot. What I've been recommending to the AAPT groups as they have written their criteria, is play some mental games with yourself.

So you have a set of criteria you're thinking about, pick a patient who's very extreme on this end, a patient who's extreme on this end, and a typical patient. Try to apply the criteria to that patient. Do you get the results that you intended?

So what you're probably going to find, if you literally take those words as they are written, is you're going to discover some problems with the way that things are worded. You're going to exclude people you didn't mean to exclude, or you're going to have criteria in there that are meaningless because everybody has it.

So, anyway, just play around with it. You really have to put some thoughts into the words that go into these. So that's it.

(Applause.)

Page 244

DR. CARR: So we're actually just about in the same time slot as we originally planned, except what we're going to do is move the group discussion until after the break. We're right on time for the 2:30-3:00 break. Then we will reconvene, and I will invite Patrick and Steve to join the other panelists so we can have an unfettered discussion.

So thank you very much, and we'll see you in 30 minutes.

(Whereupon, at 2:32 p.m., a recess was taken.)

Group Discussion

DR. CARR: Good. So as we're walking in, let me remind people, we just shuffled around the schedule because we had speakers who were scheduled either later after this panel session or tomorrow that really had things to say that were relevant to this overriding beginning question, which is how should the AAPT chronic pain dimensions be revised to provide a framework for acute pain, and whether that is taxonomy, diagnostic criteria?

For those of you who just wanted a memory

Page 245

jogger, I had listed the headlines, but we have the people who struggled and wrote these out here with us now.

So the opening question might be, is there anything missing? There's a few questions we can ask. One would be, if you pose a question saying CRPS is to chronic pain as X is to acute pain, is there an X, is there a condition that we're troubled at our inability to diagnosis or place into a crisp compartment?

So I'll start with this question. Sir?

DR. MCLEAN: The one thing that I would say is that I think that we -- at least it seems to me that it would be helpful before going into discussion to come to some agreement on the goals and the priorities of the goals. Because I think we could easily have -- you know, what the goals were will really influence what the best criteria is.

At least my concern is that if one person has, pedagogy first, and another has ontology first, and another has diagnostic criteria first,

Page 246

and we don't have any sort of prioritization of those, that we could end up going in lots of -- it could become a little circular or unclear. So at least that's my thought.

DR. CARR: I think that's a great point. Let me take a few more questions from the floor, but I'm tempted to ask you, Dr. McLean, what would your goals be? Before we do the next question.

DR. MCLEAN: I would say my own bias is that the most important thing for us that we can contribute right now is to make sure that two people studying the same condition or testing a drug on a condition are actually studying the same condition.

So creating a common diagnostic criteria is number one, and then I'm not sure about other goals after that. But again, that's just my thought, and I'm glad to go with whatever the group's thoughts are.

DR. CARR: Well, let's spend a few minutes talking about that. What is our goal? Roger, and then there was another question. Kristen. First

Page 247

of all, hear from Roger, and then Kristen.

DR. FILLINGIM: Yes. So I'm certainly limited by coming in with ideas of what the goals of this meeting are based on what the goals of our earlier meeting with AAPT were. And I think essentially there are two primary goals. One is to develop a framework that working groups can systematically use to develop diagnostic criteria for acute pain conditions and to decide what the acute pain conditions are to which that framework will be applied. That's very much what we did.

DR. MCLEAN: And the framework being the dimensions?

DR. FILLINGIM: Yes.

DR. MCLEAN: Yes.

DR. FILLINGIM: If you follow anything close to what we did, it would be the dimensions. Although, I guess this group could decide that doesn't work at all, we're going to come up with a framework that's not that at all, but a framework nonetheless.

DR. MCLEAN: But do you think that

Page 248

the -- and this is truly a question, will those dimensions depend on what the use is or what the goals are in terms of the use or the product?

DR. FILLINGIM: You mean how you want the diagnoses to be used?

DR. MCLEAN: What are the priorities for the diagnostic system in terms of its utility or application?

DR. FILLINGIM: I think that's for this group to decide, but I think it's for clinical use and for research use, to improve clinical care and to enhance research as you've talked about.

DR. MCLEAN: Yes.

DR. FILLINGIM: There's a clinical trial of X, that everybody who is studying X is studying the same thing.

DR. MCLEAN: I thought that this morning, the example of creating the classification systems and then creating diagnostic criteria that everyone would use and try to get everyone to use them was a good example of where there's a tension there.

For example, if there's just a goal of

Page 249

coming up with diagnostic criteria for fibromyalgia, based on something that everyone can agree on, then saying, okay, we're going to call it musculoskeletal versus central nervous system, you run the risk of pissing off whoever those people are in the different camps.

They're less likely to use it because you're sort of going beyond the evidence and experts' opinion to say, well, my best guess right now is that it's this category or that category, without even meaning to. But just being agnostic, but saying, oh, for now we're going to lump it over here; you could still potentially -- so there are these tensions.

DR. TURK: Can I add to that point?

DR. CARR: You can add, then I'm noticing there's Kristen, Chris Wu, and Rosemary. So we're all going to get our say.

DR. TURK: This is just a clarification. When the working groups in the AAPT come up with their criteria, they're encouraged to send these out to relevant organizations, to relevant people,

Page 250

to people who might disagree, to try to see if they could get input and potential buy in from them.

So we're well aware when you have a working group of 5 or 6 or X number of people, you're not always representing everybody out there. But the goal, the hope is to go back to the other groups, other individuals, other organizations if you know that this is a disease that's covered in the neurology area to make sure that we have the appropriate people.

So they may not agree, but at least the mandate was that they should, to the extent possible, go back to relevant groups, relevant individuals and not to -- to try to increase the buy in. Of course, they could always come up with a disagreement.

DR. CARR: Steve, why don't you add?

End of Day Wrap-Up

DR. BRUEHL: Keep in mind -- so those are excellent questions. This is a multipurpose project. It's clinical. It's research. And Bob wanted me to make sure to keep things on track

Page 251

here.

There are tangible things we have to come out with this. One is what are the dimensions we're going to use, and the other is, start to at least move down that road of thinking about what the different buckets would be that we need different core diagnostic criteria for. So if we come out of this at the end of the day tomorrow with those two things, we're good.

Now, to answer your question, some of these things that have been raised, part of the reason for this was the hodgepodge, if you look across different diagnoses, there are criteria out there for some of these; now, maybe less so in acute pain than chronic pain.

But chronic pain, it was a mess, using all different formats, some of which like TMD explicitly included psychosocial factors, which are known to have a major role in how those play out; other conditions that clearly had a role of psychosocial factors with no acknowledgement at all. And it's just everything was very different.

Page 252

The idea was to parallel DSM and put everything on a level playing field so that we're covering the same bases for every major disorder. And it's not going to be an exhaustive list of everything that might be diagnosed for acute pain, but the major conditions that are the largest problem areas or most prevalent.

So that's what we want to be thinking about is these dimensions, of these five that are up there, a good parallel for what would be appropriate for acute pain.

Do we need to add a separate dimension that addresses clinicity issues, or temporal issues, and risk for chronification, and that kind of thing, kind of like was discussed earlier, or are there things that we are totally forgetting that may be so important they should be a dimension? Or is there a dimension on here that is irrelevant for some reason to the topic of acute pain?

So be thinking about that. And the discussion, don't be afraid to challenge. Now is the time to think a little out of the box,

Page 253

challenge things. But we do have to, by the end of the day tomorrow, narrow this down to actually know what those dimensions are.

DR. DWORKIN: So Sam, the only thing I want to add is we've had two precedents that we've really drawn on. One is Steve's work with CRPS, and the other is psychiatry and the DSM-3, 4, 5.

I think it's accurate that for both of those previous efforts, research was the initial objective, using the criteria in research studies, clinical trials, drug applications. And then second was educational. And it's only once you have the education occurring that you then get widespread adoption in the clinic.

So at least using those two efforts as precedents, DSM and CRPS, I think the order of objectives would be sort of what you were saying, which is clinical research, education, the clinic.

DR. CARR: So let's go -- and Kristin, you had a comment?

DR. SCHREIBER: Actually, yeah. My comments were exactly on the things that everybody's been

Page 254

talking about. So it occurs to me that -- I mean, it's really great to have the framework of chronic pain here. However, there are some really important differences that I think impact the prioritization of how we frame what's going to be number 1, 2, 3.

Firstly, I think the most prominent is that it's not as much of a mystery the diagnosis. In most cases, I think, for acute pain, we kind of already know what the diagnosis is, and so not as much effort or emphasis needs to be put on that.

Probably more prominent should be how are we going to treat it quickly because we don't have the luxury of seeing this patient over many months and working on the diagnosis. We have to kind of see it right away, figure out what treatment is going to be best for them.

So I would argue for it being a little bit more oriented towards being able to figure out what treatments will be helpful, and then individualizing. So that's where, as I mentioned before, the 4th and 5th, and maybe then if we said

Page 255

there's a 6th, which is a time component, that those would be increased in prominence in the acute pain framework. That's just my two cents.

DR. CARR: Thank you. Chris Wu?

DR. WU: I think those are excellent comments. One consideration is the core diagnostic criteria, if that were to be removed, or if there was an argument against removing it, instead of relating it to the pain itself, would it be more appropriate to direct it to the underlying diagnosis that led to the pain, which is frequently true in acute pain diagnosis.

That seems to somewhat differentiate it from a chronic pain diagnosis, where the diagnosis is intrinsic to the pain itself; whereas here we talk about the diagnosis being intrinsic to the underlying mechanism that led to the pain.

I think that carries some important treatment connotations. For instance, if we had bone pain from a fracture, trauma versus metastatic lesion may lead to different expected treatments and functional prognoses. So it's a way of

Page 256

somewhat distancing ourselves from the first dimension, or at least modifying it to this context.

Does that seem -- can you build from that?

DR. SCHREIBER: I guess I definitely wasn't saying take out the first three. You know, I just think maybe less prominence. I don't know if we can turn it on its head. But as someone mentioned, the first thing that people will look at is the first one, and then ignore the rest, and then maybe we haven't served our purpose.

DR. CARR: Now Chris, and then we'll continue around the room.

DR. WU: Based on what I've heard, so we're interested -- the purpose of this is more, for what Bob says, initially for research, clinical research, and then we want to organize -- I mean, I don't want to use the diagnostic ability so everyone's on the same page. I understand Kristin's concern about the clinical use of this.

I'm not sure -- are we allowed not to use the 5 dimensions? We might come up with a

Page 257

different system. But ultimately, I think the challenge is that we have to serve multiple customers here, and that will be very difficult, I think, potentially in this current format that we have.

DR. CARR: Rosemary?

DR. POLOMANO: So I think I have to digest those dimensions a bit. But for me, for acute pain, to replace the thinking for the core diagnostic criteria, it's really about the pain event. So it's really about surgery, trauma, procedure.

It's not about the diagnostic criteria, isn't as much about the symptoms and the signs. There are certainly supporting data. So I would just encourage us to think about this situational -- not necessarily temporal, but situational or event stimulus for the pain.

The other thing is that when Patrick was talking -- so Patrick you can give the right names to what I'm saying in terms of the leveling. But when you think about if the strategy for

Page 258

practice -- and, again, I think this has to be useful for practice.

If you think about the strategy for practice as pain prevention as a strategy, if someone is having surgery, you would have that opportunity to look at the mediators for pain and the modifiers for pain, and address them preoperatively.

But if it's a trauma patient or it's a patient who develops something, when you can't see them before they have their pain event, then those kinds of strategies or frameworks of thinking for mediating and modifying pain are going to be different with each acute pain type based on the nature of it.

So it makes it more complex than thinking about everybody, preventing chronic pain for everybody and looking at these modifiers because you have the opportunity. For acute pain, you don't always have the pre-event opportunity, but you certainly have the post-event opportunity for understanding these mediators and modifiers.

So whatever model we do, the sequence of the

Page 259

pain has to be -- or how the pain is situated has to be part of the dimensions.

DR. BRENNAN: I had written down injury, but I like your event as broad as one of the criteria.

DR. POLOMANO: So an infectious event would be herpes zoster. I mean, I think you can actually -- for all of the acute pain I was just thinking as everyone was talking, you can fit some kind of event to it.

So maybe it needs to come first, and then maybe the dimensions, these dimensions will serve us well. But the common medical comorbidities -- so I just want to say again -- I think really needs to be thought of in terms of mediators and modifiers for pain. Depression.

DR. FILLINGIM: Let me just say, first of all, my feelings won't be hurt if you get rid of all of these components of the framework.

(Laughter.)

DR. FILLINGIM: And let me be clear, when we developed AAPT, we always intended that there would be an acute pain taxonomy, but we didn't take that

Page 260

into consideration at all when developing these. These are fully intended to serve chronic pain conditions and chronic pain conditions alone.

The process I described might be informative. Some of the other characteristics of the taxonomy might be worth considering. But I think acute pain, as you're pointing out, is in many ways a different animal, and you may need your own dimensions.

DR. POLOMANO: And I think you can align these dimensions with more relevant but similar dimensions that address, in concept, almost something that's the same.

DR. CARR: Okay. Paul, Bob, Mike, and then Srini.

DR. DESJARDINS: [Inaudible – mic off] -- and I don't know what turns these off spontaneously, but I'll go back to them when I need to.

DR. CARR: When the value of the comment declines.

(Laughter.)

Page 261

DR. DESJARDINS: Oh my God, it's off already.
(Laughter.)
DR. DESJARDINS: I found it easier to think about this when I started thinking about the kinds of questions one might want to ask. And it became obvious in the context, from my preparation looking at orofacial pain, there is never pain that shows up in the face in this area that's acute that isn't already tagged with a diagnosis.
So I like, Patrick, your comment of whatever the working diagnosis, let's start there because your job is not to define how dental pulpal pain comes up. There are criteria for doing that.
So the predictors, and again as a clinical pharmacologist looking at how I would use this, a system that could help design -- and I think I'm saying something a little bit different from what you were saying, but similar.
A system that might help me look at who is not having a -- predict who is at risk for not having a smooth recovery, what are those factors

Page 262

that I need to be thinking, in particular, how am I going to treat this differently than how I would treat every other oral surgery patient?
The other piece that I think innovators have learned, and again my last comment, is that perfect is the enemy of a good enough. And I think if we can have diagnostic criteria and a system that's good enough to launch, it will be improved, and it doesn't need to be perfect.
It will not be perfect for everyone, but if we agree out of the box that it's good enough now, then we're going to make some progress. And I think we've learned that in innovation in many different fields. So thank you.
Dan?
DR. CARR: Any comments? We'll continue then. So Bob, you had a comment?
DR. DWORKIN: Yes, okay. My first comment is regarding having a dimensional framework. And I wanted to make reference to an article by Elena Kramer in 2007, writing on whether or not DSM-5 should include dimensions still. And 25 words that

Page 263

she wrote might be helpful here for somebody who thinks we shouldn't have dimensions.
She says, "Every categorical diagnosis can be made dimensional by using symptom count, symptom duration, symptom severity, degree of impairment, certainty of diagnosis, consensus of multiple diagnoses." And then she goes on to cite a couple of specific examples that show the clear benefit to a dimensional approach.
We have not talked about genetics or epigenetics, but I think that a comment was just briefly made that when we go on rounds and we see the patient with acute pain, we know what the diagnosis is, and I couldn't disagree with that more.
I think if we knew what the diagnosis was every time, then every time we saw a patient, we would be able to prescribe the right treatment and it would work. Instead, I think we kind of figure out what some of the possibilities are based on what does and doesn't work. So I think we can't be glib about knowing.

Page 264

Last is the piece about acute and chronic pain. They're both pain. And I thought that excellent discussion about with the boxes and the methods of steering and braking that Patrick led is very useful.
For those people who might be passionate about how chronic and acute pain might be connected, I think if we design two different systems to study them, it will make them much harder to connect. And I think there's a strong advantage, and I would strongly support that we adopt the same basic framework that was used for the AAPT.
DR. CARR: Thank you.
Let's see, over in the back and then Srini, do you still have a comment? Okay, back, Srini, Mike, Mark, Henrik, and Santhanam.
MALE SPEAKER: Well, I think the diagnostic part really dramatically varies depending what it is. So if someone presents with the first onset of right lower quadrant severe pain, there's a pretty good differential diagnosis there. And it could be

Page 265

anything from an ovary to appendix. So a wide range of things and the diagnostic criteria that lead you to come up with a diagnosis really matter.

If they had imaging that demonstrated a lesion that required surgical exploration to determine what type of lesion it was, and they had zero pain beforehand, and they have an incision, they had surgery, that's pretty easy diagnostic criteria.

So those seem like very different things. They're both acute pain, but they're really quite different. And the emphasis on kind of the context in which the pain occurs really, really is what matters the most.

If that person having surgery had pre-operative pain that was in the exact same area where they're having their pain, they're quite different than the person who didn't have pain beforehand.

Then sometimes even if we know the diagnosis, the type of pain the person is experiencing could be quite different. My example

Page 266

is rib fractures. Someone has a rib fracture, sometimes it's very specific point pain right where the rib is fractured. Sometimes it's a generic kind of pleural hemithorax kind of pain. Other times it's very much intercostal neuralgia like. Those are all related to that rib fracture and that rib trauma, but they're three very different types of pain.

So there's a lot there, and the diagnostic criteria may be really important for one and not so important for the other. But it seems like the context is what we need to really lay out first.

DR. CARR: Okay, I think, Mark, that you were next. And we'll do the best we can, but everybody who has something to say will be called on.

DR. SCHUMACHER: Right, thank you. So again, struggling with the 5 domains but wanting to retain the structure as mentioned, I had discussed this briefly with a few folks during the breaks, is that potentially the last three, and maybe if you added tissue site, maybe plus or minus visceral

Page 267

involvement -- so the idea that possibly the last three represent modifications or modifiers, and depending on their weight, if you have strong evidence, that could then kind of jump the queue to solidify your diagnosis.

So I look at the rest of those as perhaps the flexibility we're looking for in terms of coming up with the value of a diagnosis or not. And it could also integrate other aspects that have been mentioned about genetic testing or all this other, which becomes more the precision medicine as time goes on.

So not fully thought out, and not to be made overly complicated, but it just seems like these are modifiers to the primary issue. Thank you.

DR. RAJA: So I was trying to think of what is so unique and different about acute pain compared to chronic pain. And many of you have talked about an acute event or injury initiating the pain. And Tim, in your discussion you clearly indicated that the mechanisms for injury to -- or pain resulting from injury to, say, muscles and

Page 268

tendons, or bone, or neuro, may be very different.

So somehow, I'm looking at this dimension, and the nature of the tissue involved in this injury process resulting in acute pain doesn't seem to come out. And maybe that's something that needs to broaden into this dimension for acute pain.

DR. CARR: Mike and then Henrik.

DR. KENT: Sure, thanks. So I'm also struggling with the 5 dimensions, but I agree with Bob in terms of adapting some format. I'm just wondering, initially, we were talking about let's see how well the 5 dimensions fit, and then talk about buckets. And I think we've had some comments about events, focusing on tissue injuries.

I'm wondering by having that slide up there if we've just become cognitively locked, not to the dimensions but the words of the dimensions.

In the form of high school football, I was just wondering if more of a chalk talk type scenario, should we just bring the slide down and actually start from what Pat was talking about, the objects, start talk a little bit about do we want

Page 269

an event, do we want to talk about tissue injury, and then just start -- not start fresh, but start fresh and just start listing dimensions. And then put the slide back up and see how similar or different we are, just as a way to move forward a little bit.

DR. CARR: So we're all okay taking them down? So can you just take the slide off for a moment.

DR. KENT: By the way, I did not play high school football.

(Laughter.)

DR. CARR: So Henrik, you've now had a chance to absorb a lot of these comments. What do you think?

DR. KEHLET: Well, first of all, the diagnostic, I think when you look at the post-op pain literature, we still see a lot of studies where it's just pain and it's rated. It should be diagnosed exactly in relation to anatomical function; I mean, movement associated pain. That's the first thing.

Page 270

Then I think we should use Tim's proposal because you elegantly showed transduction mediated pain, inflammatory, mechanically, ischemic, et cetera, et cetera. That goes into the diagnosis.

When it comes to the comorbidities and risk factors, again, it's really important to have pre-injury pain at the site of injury or pain at other places in the body. It's crucial. Opioid using before the injury catastrophizes and also assessment of the nociceptive function, if it possible, at least before operating. Are these high pain responders or not? That's extremely important.

But the most important is really what is the consequence of the acute pain. And if you have 8 on your best scale after tensile operation, it doesn't threaten your life. If you have 8 after a colonic section, it may threaten your life. So we need to have the functional consequences of the pain assessed in detail; in detail.

DR. CARR: Thank you very much.

Page 271

Any comments on that comment?

MALE SPEAKER: Dan, I don't know if it's premature, but I just want to follow up on that, and we discussed this during the break, and that is this concept of defining what high impact acute pain would be.

There's an analogy to this because we took this on in the National Pain Strategy, and one of the working groups there, the population research working group for the NPS, under Michael Van Korff's leadership and Ann Scher, we worked together to define high impact chronic pain.

We recognized that the driver from this was the HRQ data, which shows that in our country, 1 percent of the patients utilize 23 percent of our healthcare resources; 5 percent of our patients utilize over half of our resources. So there's a small sliver of people that are accounting for the big impact from a societal burden.

Apropos, Dan's use of Gertrude Stein's, "For a difference to be a difference, it has to make a difference," one thing this group could come out

Page 272

with is something that defines that group of people that really make a difference.

We defined high impact chronic pain in the National Pain Strategy as chronic pain associated with substantial restrictions of participation in work, social, and self-care activities for 6 months of more.

One could readily come up with a definition here of high impact acute pain and be able to use that to separate the people that Henrik just talked about, those two groups of people, one whom you know might have a high pain score, but they're not going to go on to have high impact chronic pain -- high impact acute pain, the other one, who would.

So I would put that forward as something very tangible this group could define.

DR. CARR: Well, if I could add a comment. I think, to me, that is an attractive idea because in the daily world of practice, we already now have many clinical pathways that are established that work pretty well for most people and do not need

Page 273

continual observation and monitoring by physicians. There are nurse-led pain services that do absolutely fine.

So it would be possible to invest a lot of time and energy and thought into elements that are not really problematic, that no one really is interested in improving because they work pretty well.

So there might be some starting point to begin with, what Henrik has mentioned and what you're saying, that we should be concerned with improvement and where are the areas for improvement the vexatious high cost small minority or the ones whose life is at risk. So we should stratify our own efforts according to the importance of the target.

I don't know how that's -- it's somewhat of a departure. It's a little bit different than the chronic pain or the AA. But how do the AAPT people feel about that? Dennis or Bob?

MALE SPEAKER: Well, so Dan, Sean, I'm not sure how that maps onto diagnostic criteria. If I

Page 274

want to do a clinical trial of shingles pain or acute post-operative pain following herniorrhaphy, I need to have inclusion/exclusion criteria. And even if those types of acute pain don't have a high societal impact, is this going to provide me with guidance in doing a clinical trial?

So I hate to sound like a broken record, but I think of most things in terms of their implications for clinical trials.

DR. BRUEHL: Segue from that. So thinking about the -- I'm not going to call them Dimensions 3 through 5, or 2 through 5 as we had them up there before, but what was mentioned earlier, I think about creating dimensionality out of these other dimensions.

So instead of just categorical yes/no does the patient have this, those issues of who is the high-risk patient, if we structure it right in Dimensions 2 through 5, simply assessing each of those areas, you would have -- like an MMPI profile where you've got dot, dot, dot, dot, 5 dimensions, and you've got certain patients, if they're here,

Page 275

very high here, low on this and high on this, that patient is going to be a problem.

So we would hope that however these 5 dimensions are laid out, that that would allow you to do exactly what Sean and everybody else has kind of mentioned about those high burden patients or high-risk patients, those patients that are difficult to treat effectively.

I keep hearing this idea of wanting to use these criteria to predict. We want to know what's going to happen -- we want to profile them, know what their course is going to be, and based on that knowledge of what's likely to happen, be able to intervene early before they ever get there. And I think that could be captured if you pick the right dimensions, and I think that's what our task is, isn't it?

Just so you know why I'm standing up here is because I want to get -- we've got 45 minutes left, officially, and I wanted to start taking some notes if people want to throw out some suggestions for dimensions. And one thing just before I forget

Page 276

this.

So back to the issue on Dimension 1, two things. One is, we are not diagnosing disease, okay. So while the pain, acute pain may be due to pancreatitis, we are not creating diagnostic criteria for pancreatitis.

I'm just telling you what the parallel is in the chronic pain. Now, you could choose to do differently. But in the chronic pain setting, we were going to just say that whatever group specializes in pancreatitis has their certain criteria.

So these are pain criteria. So what we would say is, make reference in the diagnostic criteria, has been diagnosed with pancreatitis according to blah, and then you got your pain characteristics. And I agree with the comment earlier that some conditions, there's going to be very little to describe the pain other than just it's intense. There aren't a lot of other characteristics.

I want to go back to Trip's comment earlier

Page 277

about diagnosing acute neuropathic pain versus non-neuropathic pain. Clearly, there are differences in presentation between certain types of chronic pain conditions.

When you're coming up with that Dimension 1, which really does need to be about making that dichotomous diagnosis, that's where you want to capture whatever those differences are that when you see a patient, you would go, this is an indicator that X is going on. In this patient, I can see this pattern. They've got Y going on.

So that said, I'll go back to Dan to answer questions. But pretty quickly here, let's try to get to just brainstorming at least some possibilities for the 5 dimensions or however many you've got.

DR. DWORKIN: Temporal trajectories.

DR. BRUEHL: Temporal trajectories.

Dr. Wu?

DR. WU: Essentially, maybe we could just not even worry about whether it's 1, 2, 3, 4 or 5, but just like temporal trajectory, event,

Page 278

mechanism, all the things we've been talking about, characteristics.

FEMALE SPEAKER: Inciting event.

DR. BRUEHL: I'm just going to call it event. That could be a disease. It could be whatever.

FEMALE SPEAKER: Preventable or not preventable.

DR. BRUEHL: What?

FEMALE SPEAKER: Preventable or not preventable.

DR. BRUEHL: Okay.

FEMALE SPEAKER: It's like a trajectory.

DR. BRUEHL: Because what is preventable? The pain?

FEMALE SPEAKER: Like because we're saying some things are going to fall in one category versus the other. Some things will already be going on, and some things are going to be something that's happening in the future.

DR. BRUEHL: So preexisting or not?

FEMALE SPEAKER: Yes. At the time of

Page 279

diagnosis. Maybe this is not a dimension.

DR. BRUEHL: Okay. Put that on the table for now. There were a couple of others. I'm sorry you said the temporal --

MALE SPEAKER: Trajectory.

DR. BRUEHL: Temporal trajectory.

MALE SPEAKER: Steve, I'll put in -- I put locations, organ or tissue.

DR. BRUEHL: Okay.

MALE SPEAKER: All one.

MALE SPEAKER: What about organ system involved?

DR. BRUEHL: Would that fall under locations, organ system all as one?

MALE SPEAKER: Are we at the level of trying to say like characteristics is one, or should we say more things like quality and intensity? I'm not sure quite what layer to go to with this. Whether just characteristics is -- or whether we should get more granular than that at this point.

DR. BRUEHL: I think that's a good broad term, and we don't have to decide what those

Page 280

characteristics are, and that may vary from condition to condition. But you're talking about pain qualities in some way. Yes.

MALE SPEAKER: How about modulating conditions? Very broadly and you could subclassify different domains of modulating conditions.

DR. BRUEHL: Okay. And when you're saying modulating conditions, are you talking about medical conditions, psychological state, what?

MALE SPEAKER: All of the above, so you'd have to have subclasses to describe the cohort of things that could modify the presentation.

DR. CARR: Did you have functional interference?

DR. BRUEHL: Not yet.

MALE SPEAKER: And I think you want to have the degree of trauma, or degree of inciting event that caused the acute pain, so you can say the event and degree.

DR. BRUEHL: Okay. Quantified somehow.

MALE SPEAKER: Correct.

MALE SPEAKER: I know this is not mentioned

Page 281

about trying to look at events, but in terms of diagnosis, but I think we have to finally link this up with some kind of ICD-10 that Sean talked about in the morning. That's very critical as well, because that's how you finally put all this information back into the electronic medical records.

So I know it's not what you're doing right now, but I think ICD-10 is something critical that we need to talk about.

DR. BRUEHL: : Put that in the parking lot.

I don't know -- could I just say I don't know what the degree of the event -- what does that mean?

MALE SPEAKER: Can you give an example?

MALE SPEAKER: Yes, so essentially, I mean it could be a skin abrasion that can cause acute pain. Or you could have a huge fracture of 10 bones that's causing the event. So what Tim talked about, Tim Brennan talked about, the degree of injury, which kind of tissues are injured would make the degree of the acute pain mentioned --

Page 282

MALE SPEAKER: Wouldn't that go under the organ tissue system?

DR. BRUEHL: Okay, let me ask, is that extent? For example, like we had the incision example earlier, where a small incision and a large incision didn't make a difference. But if we're talking about multiple bones versus one bone, does that make a difference, and is that a way to objectively quantify something like this? Is that kind of what you're talking about?

MALE SPEAKER: Can I just say in that regard as someone who studies acute and chronic pain after sexual assault, most rape survivors who show up at the emergency department in the United States have moderate to severe pain in four or more body regions. And the great majority of it is not in areas where they were physically traumatized, so the stressed induced type analgesia, and we see it in BC [indiscernible] and so forth.

So I get very nervous about this extent as because stress-induced type analgesia doesn't seem to obey those rules.

Page 283

DR. BRUEHL: Okay, so --

DR. TIGHE: As a contrary point, though, I do like that model [indiscernible], inflammation, and sepsis. We're talking about high impact pain, where you can have poison ivy all the way to a septic event that can lead to the same mediator threatening the life of the organism.

So there are parallel models in other disease states that I think it's worth considering for extent. I don't know how you quantify that, though, in pain.

DR. KEHLET: So I want to go back to Kumar's parking lot again, the ICD-10, just for one reason.

DR. BRUEHL: I've got to put it down here.

(Laughter.)

DR. KEHLET: Okay. But it is Kumar's parking lot, by the way. The important thing to realize is the ICD-10 also gives us criteria for whether the operation was done arthroscopically, laparoscopically. Those things are going to matter a lot in terms of predicting your pain and your management of pain.

Page 284

So if we take that out of the equation, how does that help? I mean, an event is an event, but then the intervention, especially post-surgical, is going to be completely different if it is laparoscopic versus an open laparotomy.

MALE SPEAKER: Then that is one issue. So we at some point would have to start thinking about how you characterize the event. It kind of gets back to the classes and subclasses and all that.

So if you've got surgery as the big class, and then you have -- I'm blanking on examples right now, but you've got something like -- you've got lumbar surgery, and now you've got microdiscectomy. You can narrow it down more and more.

DR. BUCKENMAIER: Well, I kind of like this idea of looking at organ systems and maybe percentage involvement because this idea of ICD-9 breaks down the trauma. And certainly, a soldier with a polytrauma is very different.

MALE SPEAKER: You have to use the mic.

DR. BUCKENMAIER: I'm sorry. I'm not used to using a mic because usually most people ask me

Page 285

not to.
I think this idea of a soldier with polytrauma as opposed to an isolated trauma, we see very big differences just like the scale of surgery. The analogy that was used was laparoscopic cholecystectomy versus an open cholecystectomy. Certainly, more tissue is involved in an open cholecystectomy, more organs involved than with a laparoscopic.
So I would agree that my concern as an anesthesiologist for these two patients would be different from a pain perspective. And that's certainly the case in actual trauma, where you're dealing with a 3 or 4-limb amputee with multiple system involvement as opposed to somebody that has a light injury, they've just lost an ankle.
DR. TIGHE: So one comment on the ICD-10. It does allow us both procedural and diagnostic, and it does allow a roll up. It in itself is ontologically organized. However, I don't think it's designed to encompass all of the dimensions. So it may be useful as an entry for a triggering

Page 286

event or something similar, but I don't think it's going to encompass some of the other domains.
The other issue is that many of our patients will come in with multiple diagnoses. We keep track of 50 simultaneously. So then you'd have to keep track of are we looking at primary diagnoses, the first 10, the first 50? What if they resolved? So it does get a little bit tricky. I don't think we can just say we'll include ICD-10, but it does carry a lot of value if appropriately contextualized in this.
MALE SPEAKER: But for event, should we -- I mean, do we need to go back even further from laparoscopic pain after choly? Back to Dr. Brennan's talk, do we need to go back even further to the tissue, that's not organ system but the tissue that's involved, a bone versus parietal pleura, versus lung tissue.
A good example that Brett gave is you compare visceral pain. Well, that's not a diagnosis, but pain after gall bladder isn't really a diagnosis either but it's very specific.

Page 287

So are we getting stuck on focusing -- are we equating event to diagnosis, or do we need to take a step back further as the group -- is there any capability to be more of a tissue injury, whatever that etiology is, inflammatory, neuropathic? Just a thought to throw out there.
FEMALE SPEAKER: Could I just comment on that? In many surgeries or injuries, there's going to be multiple tissues involved, so that just sort of messes up that as an organizing principle.
MALE SPEAKER: But I don't necessarily think it does mess it up as an organizing principle because I don't think you need to start -- I don't think Dimension 1 needs to start at the peak of the pyramid.
So if I have a femur fracture and I get it fixed, it's bone pain. They probably cut through a nerve, it's nerve pain, muscle. But that all plays into a classification system not necessarily to lead to the diagnosis, but to classify the complex array of that acute pain experience. So it's complicated, but I think it's essential.

Page 288

DR. BRUEHL: I'm thinking what you just said there, those different aspects of the injury, to me, all would be tapping into, kind of jointly into the degree or extent and the organ system issues.
I think those are -- it sounds like what everybody is saying is that that is pretty critical to understanding how seriously we need to take pain for a given patient because there are clearly a lot of differences, and some would be very low extent and low severity, and all that, and others very high, who were probably the ones at high risk for complications on down the road.
So I think it's important to look at all this. I'm not sure how it's going to be organized, but it's great. Keep throwing them out.
DR. BRENNAN: Steve, is keeping it early on, Steve and Roger, keeping it broad early, and then catching tissue differences that may occur, as Mike points out, further on down the line an approach that fit with your previous work? If it starts really broad, it will catch a contusion with or without fracture that are very different.

Page 289

DR. BRUEHL: Are you saying that the way the criteria that we would propose or worded would be broad or specific?

DR. BRENNAN: Keeping it broad at the --

DR. BRUEHL: Dimension 1 level.

DR. BRENNAN: Not at the level, but just if we end up with 7 dimensions, the broader they are, the more likely we're going to --

DR. BRUEHL: Yes, that's good. I agree.

DR. FILLINGIM: And I wanted to get back to this event thing, and there's a lot of focus on tissue. But as Sam points out, there are other aspects to the severity of the event from the psychological meaning of the event, be it motor vehicle accident or sexual assault, where the tissues involved in the event seem to be far less important that other aspects of the event severity.

But that could still be -- so the way these dimensions will play out for different conditions will be sort of coded differently, or the way it gets filled in will be somewhat different. So that relates to the broadness. So these dimensions need

Page 290

to be broad enough to incorporate that kind of variability across conditions.

MALE SPEAKER: There's no evidence that -- if we're talking about neuropsychiatric sequelae or disorders of the brain or nervous system, as a population, that more trauma equals more outcomes. PTSD rates are just as high among people discharged from the emergency department as they are among those admitted.

There's just this huge variation there, so I think that's really important to keep in mind, that greater tissue injury outside the OR has very little to no correlation with risk of chronification across [indiscernible].

DR. BRUEHL: Can I just ask, are there protective effects? Some people -- like they both have similar injury, both have PTSD, one gets better and one goes on to have a horrible outcome --

MALE SPEAKER: We know in the emergency department, expectations of recovery -- Roger and I have a paper working on that, that we know that you

Page 291

know comorbid psychological symptoms, those types of things, the things that we would expect from the pain literature.

DR. BRUEHL: Okay. And that's under modulating conditions as we have it up here, right? Yes.

Steve, then we'll do Bernie.

DR. RAJA: One aspect in acute pain, which has significant therapeutic implications that needs to be brought in, it may come under Dimension 5 that was in the chronic pain, and that is prior comorbidity and therapy.

For example, a patient on 100 milligrams of methadone pre-op because of a drug abuse issue post-operative after surgery is a totally different acute pain patient than one who has never seen opioids before. So somehow building that into the acute pain taxonomy is probably important.

DR. BRUEHL: That sounds kind of like the -- for chronic pain, it was common medical comorbidities, but I think maybe for acute pain, it is more the condition existing prior to the injury

Page 292

that we're talking about in the event here. It was ongoing at that time, right? Yeah.

Steve?

STEVE: I would say -- I know we're talking about surgery in like big traumas, but if we take acute pain, extensor tendinopathy like elbow pain let's say, it's a big difference if it's a work related versus sport related, you know, those types of things. So more of the context, I think maybe that's within that Dimension 3.

DR. BRUEHL: This is like psychosocial legal context.

STEVE: But it also can have a physiologic effect too. Yeah. And that could also be protective because if it's work related, but they have a strong relationship with their boss and a positive outcome about their job, that's a better outcome. So yeah, I think that whole context of it with the injury.

DR. BRUEHL: Okay. And you said medical also? Is that kind of primarily bias, or psychosocial, and legal?

Page 293

STEVE: No, in an underlying context. So again, was it work related, was it while they were running.
DR. BRUEHL: Okay.
MALE SPEAKER: And I think event is -- one thing about event is it's kind of a shorthand for that.
STEVE: Yeah.
MALE SPEAKER: You know, which doesn't capture all of it, as you're pointing out, like work related or not. But a lot of it we know --
STEVE: Then you take a deeper dive in it.
MALE SPEAKER: Like when you say a rape versus car crash versus this, you learn a lot about it.
STEVE: Yeah.
DR. BRUEHL: So this is the context of the event, or I guess it would be the context of the pain, too, because the event and the pain are kind of inextricably linked in here.
DR. FILLINGIM: Well, but it sounds to me like a combination of the event, is this a work

Page 294

related injury or a sports injury, but then also sort of modulating modifying factors that are present, that might be around the event, but might be completely independent of the event. These people are independently wealthy, and so they don't need a settlement. So it's sort of combination of the event as well as --
STEVE: Maybe those are --
(Crosstalk.)
DR. FILLINGIM: -- factors.
STEVE: -- interrelated do you think?
DR. FILLINGIM: Yeah.
STEVE: The modulating conditions and the context.
MALE SPEAKER: Steve, I'm not following. The prior conditions and comorbidities, are you talking about prior pain conditions and pain comorbidities?
DR. BRUEHL: No.
MALE SPEAKER: You're talking about medical or --
DR. BRUEHL: Well, opioid use. I don't

Page 295

know, does it go beyond that? Other medical conditions.
MALE SPEAKER: Because I think they're distinct concepts, right. Like there's the comorbid medical conditions, and then there are pain comorbidities.
DR. BRUEHL: Yeah.
MALE SPEAKER: And I think that they're very distinct here.
DR. BRUEHL: Do you have a preferred way to word it that would be clear?
MALE SPEAKER: Well, I didn't know what you -- but you made it sound like that was coming from some -- like you have talked about this before, prior comorbidities, that this was part of your past taxonomy work.
DR. BRUEHL: No. This is talking about conditions, comorbidities present at the time of injury, of the event.
MALE SPEAKER: I think that when we talk about pain specifically, does the chronic overlapping conditions become very important?

Page 296

DR. BRUEHL: Right. So prior chronic pain would be a context that's --
MALE SPEAKER: But even more than just chronic pain. I mean these chronic overlapping conditions, what we would call centralized pain. I mean, much to the chagrin of some in the room, we would call it centralized pain. Those I would say are important, and there are ways to assess that.
MALE SPEAKER: So do you think that's comorbid or a modulating factor?
MALE SPEAKER: It depends on what you're treating the person for that day. So I would say --
MALE SPEAKER: Ankle fracture.
MALE SPEAKER: Yeah. I mean, I think that is a comorbid condition.
MALE SPEAKER: So I mentioned before about how I'm not as good a diagnostician as some other people, and I find that treatment informs my diagnosis more often than I wish.
I don't know how that would be codified in this listing, whether it was response to initial

Page 297

treatment or yes or no, or whether you know a WHO 3-step approach failed or succeeded. But in some way, I think that building in a response to treatment might be helpful.

DR. BRUEHL: I think that makes some rational sense. What it implies is the diagnosis isn't static but it's a feedback process. You make a diagnosis initially, and maybe that would be blank at that time. You try some things, and then you would have to revise the diagnosis, at least that dimension based on their response. And under extreme circumstances, maybe their lack of response would change your diagnosis.

I guess it's open to the group as to whether that makes sense to do that. So response to treatment, so it would not be available at the time you make the initial diagnosis, though.

MALE SPEAKER: Well, it would be because most -- very few of us, even those on the front line, aren't necessarily the first responder.

DR. BRUEHL: Okay.

MALE SPEAKER: So something might have been

Page 298

done.

DR. BRUEHL: Okay. I'll put it down here.

MALE SPEAKER: For example, it would have the ability to identify a condition that was not easily treatable if you broke the treatment down and it didn't work, and you found that no treatment most of the time.

DR. BRUEHL: Okay.

FEMALE SPEAKER: I don't know exactly where this would fit, but I think it's probably important. And this sort of gets to like -- or hopefully it would capture the times when the diagnosis is uncertain and is potentially much more serious, like you just had surgery now you have abdominal pain, and it might be an anastomotic leak, or your lung may have collapsed, or I don't know,

Where would we -- would that be under context maybe? I kind of feel like pain is almost always worse for people when it represents something unknown to them. If they know, oh, well, I'm having pain because of X, this acute pain

Page 299

because of X, they're not as concerned about it, we're not as concerned about it.

So I don't know. I'm not necessarily saying anything. I'm just throwing out a question.

MALE SPEAKER: Could I comment on that, too?

DR. BRUEHL: Sure.

MALE SPEAKER: So what Robert or Bob said I think has relevance here. Previous experience with the same or similar conditions or treatments is very relevant to the current diagnosis and treatment. So it may not be the response in the emergency room or the vehicle, but I've had this before; or even more telling, I've had this condition before but this is worse, or this is different. These can be very telling. I don't know how you're going to categorize that.

But I did have another comment, and that goes to the utility of these different criteria. Because while the criteria may apply to the clinician in the diagnostic and therapeutic setting, they also apply to the clinical investigator in the research setting, but for

Page 300

different reasons and different uses.

So that's why I like the idea that Tim had of using broad categories here. And then when we write this up, what we include here for the clinician in ruling out or in certain diagnoses may be exactly what we want to rule out of a clinical trial because it would confound the evaluation of therapeutic response.

So that's the next step I think, which is to take these broad criteria and say, what is the utility for each of the two major purposes?

DR. BRUEHL: Right. And keep in mind, just for terminology, these are not only the criteria, these are the dimensions that we would be looking at. But yes, I agree. Steve?

MALE SPEAKER: And I just want to say one quick thing. In practice, Dimension 1, assuming it's actual diagnostic criteria, that may indeed be as far as some people go.

I think what you have to think about this, though, is that each patient, if this was done thoroughly, covering all 5 dimensions, you would

Page 301

have a really nice description of everything you need to know about that patient that is relevant to the pain. That's kind of what we want to end up with at this, because that could be used to plan treatment, track treatment, et cetera.

I'm sorry, go ahead. Dan?

DR. CARR: I was just going to say in trying to think of categories, I'm not wedded to this, but thinking about population based, you might have event, host, environment, pathophysiology, and impact. I'm trying to span with broad terms the concepts that people have talked about in the last hour. So it would be event, that is pain event, host, environment, pathophysiology.

DR. BRUEHL: I'm sorry, event, host --

DR. CARR: Event. The next one would be host, like in public health, you speak of host factors for vectors, so host meaning patient. Environment. Pathophysiology. And impact.

So I think those are broad. I don't think of things that people have brought up, like your points Henrik, I think they could fit in here

Page 302

somewhere to try to make a foundation for the most comprehensive and potentially most granular.

DR. BRUEHL: What's the last one again?

DR. CARR: Impact.

DR. BRUEHL: Impact.

DR. BRENNAN: I think impact relates to consequences that -- functional consequences that Henrik brought up.

DR. BRUEHL: So we have the functional interference up here.

DR. CARR: I would say functional interference -- instead of impact, functional interference.

DR. BRUEHL: Yeah. All right, I'll add also impact there.

Yes?

MALE SPEAKER: [Inaudible - off mic] -- degree of the physical injury, we talked about. It could be physical injury. We can say skin, muscle, bone, nerves, and vasculature, and visceral organs is actually they may present differently. And we need x-ray for one, we need

Page 303

physical exam for the other one, or just differential diagnosis for visceral injury.

On the next line after degree of the physical injury, we have pain processing, a spectrum or host dimension, personality, catastrophizing, pain experience, influence of the second person, like a family member or a surgeon. That's a very big influence, the way that the experience the pain or define the pain.

Response to medication or basically response to opioid is another thing. That depends on genetics, all the side effects that the patient may experience. It could be too good. It could be no response at all. I mean, oftentimes we get called because patient has too good response to opioid rather than not responding to opioid.

Functionality or mobility is I think the ultimate thing that we get worried about the patient that has severe pain and is not moving, rather than a patient defining like severe pain but continue to move and continue to function. That's like kind of putting it in summary.

Page 304

DR. BRUEHL: What do you mean when you say pain processing?

MALE SPEAKER: I mean the same thing as Dr. Carr said, host. Pain processing is that the same pain in two different persons may actually be realized differently or expressed differently.

DR. BRUEHL: So how would we put that if it were to be part of the dimension? Because it has to be clear to people who weren't sitting in this room talking about this. Are we talking about pain sensitivity or -- to the extent that we can assess that.

MALE SPEAKER: Pain experience is one good way to put it. The patient had a bad experience with the pain in the past.

DR. BRUEHL: Okay. So we had here previous experience with the same condition.

MALE SPEAKER: Or any condition that is painful.

DR. BRUEHL: Any pain. Okay. So previous pain experience.

MALE SPEAKER: Yes.

Page 305

DR. BRUEHL: Okay.
MALE SPEAKER: If we follow Dan's proposal, before the event, we had pre-event risk factors, and we repeat ourselves. It's clear from the scientific literature that catastrophizers, anxiety, and those things, the pre-operative opioid, or pre-injury opioid treatment, how is your nociceptive function before the injury, are you a pain sensitizer, expectations; and then pre-injury pain in the area where you have the injury versus pain in other places in the body. It's easy. It's easy.
DR. CARR: So would you accept those under host? Those are host.
MALE SPEAKER: What?
DR. CARR: Those are the factors of the host, or the patient.
MALE SPEAKER: Yes, but that's pre-event risk factors.
DR. CARR: Yes, which would also include age and gender, for example.
MALE SPEAKER: No, it doesn't matter. You

Page 306

cannot change it, and it doesn't matter.
DR. BRUEHL: I'm going to play devil's advocate here. So here is a pragmatic problem. So the patient comes in, let's just say has surgery, and you're seeing them after surgery. And now they've developed this pain, and you're diagnosing it. And it says you're supposed to identify their pre-event catastrophizing.
How do you go about knowing what happened before this ever developed, if they had never not been assessed for that specifically.
FEMALE SPEAKER: Well, I think in that situation, it wouldn't -- I mean, it would be nice to know what it was, but it wouldn't really matter. You would look at whether they were catastrophizing right then, and see, oh, the host is catastrophizing. So therefore, I may need to employ a different strategy.
DR. BRUEHL: Okay.
MALE SPEAKER: Those are different measurements, too. I mean, the pre-event pain catastrophizing evaluation will have a different

Page 307

outcome. Those 26 points will be different than at the time of the pain itself; that's for sure. So you have to deal with what you have.
MALE SPEAKER: You would think.
MALE SPEAKER: But part of this exercise is to help for future scientific trials of analgesics. And we have to have enriched analgesic trials in the future. That means that we have to stratify exactly for these pre-event, well-known risk factors so that we can focus on the relevant patient groups and forget about those who are irrelevant and they are easy to manage.
DR. BRUEHL: So really, instead of saying pre-event risk factors, if we just call it risk factors globally, it does not sound much different than what we had in the AAPT dimensions. That is Dimension 5 I think, yes.
Roger?
DR. FILLINGIM: And I think just like in chronic pain, if we just met them, we don't know what their premorbid risk factors were. We can rely on their history or other factors. So just

Page 308

because some of this stuff is difficult on the ground doesn't mean it's not important. And there will be circumstances, certainly more so with acute pain trials, where we can actually gather information before the pain starts.
DR. RAJA: Still I like the concept of host and host risk factors. And although Tim's didn't want to consider immune function as an important thing, I can think of a scenario where a patient with acute zoster with an HIV who has low immune function will have a much more intense acute pain than one with normal immune function. So host risk factor with immune function as one of the modifiers may be important criteria.
DR. BRUEHL: So the host is physiological conditions potentially. It's psychological potentially. Social potentially, in a sense, because it's the interactions with the environment.
FEMALE SPEAKER: Experience.
DR. BRUEHL: Experience too.
MALE SPEAKER: It's experience, too, absolutely. I like the term host.

Page 309

FEMALE SPEAKER: [Inaudible -- Off mic].
DR. BRUEHL: Oh, sorry. I'm trying to leave space. So we added risk factors, which would be the far left. Then we have the event, the host, which is the patient. We have the environment. We have pathophysiology and impact.
Pathophysiology, Tim, in this model with pathophysiology, would that be the TRP V1 [ph] -- what level are we talking about if we're talking about pathophysiology there would you think?
DR. BRENNAN: I think if it's broad enough, it can go to any level you'd like to because I think in some of these disease states, we might be able to take it to that. I think in an autoimmune condition that's associated with pain, it can go down to a molecule in a biologic. So I think as broad as we can keep it --
DR. BRUEHL: Okay.
DR. BRENNAN: -- so that we can get it to the receptor if we need to.
DR. BRUEHL: And this is the pain

Page 310

pathophysiology, not the associated disease pathophysiology.
DR. BRENNAN: No. We still have some that will eliminate pain based on biologics. So I think in the future, it will be valuable to be broad in that way.
DR. TIGHE: I think also if we keep it broad, we can always narrow later within that domain. We can subclass and such, so we don't have to have an absolute definition at this stage. We give ourselves some wiggle room in the future.
MALE SPEAKER: Just to think out loud and play devil's advocate for a second, I wonder whether event, host, environment, pathophysiology, where people using this system wouldn't know whether, okay, the host factor, that could be the -- well there's no characteristics in there in terms of diagnostic criteria, although they could be like let's say that we're going to have core diagnostic criteria.
DR. BRUEHL: Separate from that.
MALE SPEAKER: Separate from that, so it

Page 311

would be an additional dimension. And then if it was host -- so if the person had a history of high catastrophizing, I guess that could affect the pathophysiology of the pain as well as be a characteristic of themselves, and it could be related to their environment if they catastrophize because of some psychosocial situation.
Again, these terms may well be as good as any. I'm just trying to think about future users and them knowing what goes where, and if there's any terms or other things we should consider that might be more self-evident.
DR. BRUEHL: We can break down into these categories and rename them, just use them conceptually to lump together things. I think that's totally fine.
MALE SPEAKER: And we need an acronym, too.
DR. BRUEHL: Bob is working on that tonight.
DR. CARR: Well, just to clarify, though, for pathophysiology, we could by convention put different things in different compartments. But I was trying to respond to Tim's challenge to keep

Page 312

the things broad. And pathophysiology, to me, could include your very good point about which tissue, which tissue type was affected. What was the location? What are the putative mediators of that particular configuration?
DR. BRUEHL: So I think mapping -- and we're not locked into this, but I was just thinking, I can't do it right this second, but it may be worthwhile listing the event, host, environment, pathophysiology, impact, and then mapping the other things that we've said here onto that. It would be valuable to do that.
Would you mind if I take down the paper in order to write on another one?
MALE SPEAKER: Go right ahead.
MALE SPEAKER: There's a charge.
DR. BRUEHL: Well, I mean, is anybody actually reading this and relying on this to make some comment right now?
Knox, go ahead.
DR. TODD: You're welcome to go to the next page.

Page 313

DR. BRUEHL: Okay.
DR. TODD: But there is a charge.
(Crosstalk.)
DR. BRUEHL: That's right, I didn't realize it was a post-it note.
DR. TODD: So one of the things I've been thinking about in listing to the conversation, and perhaps this is just a contextual factor, Sean and I were talking about rapid learning systems and how users would use this information to modify our healthcare systems.
So as a patient comes in, private pain becomes public assuming it's not an overt injury, and there's a transaction between the patient and a clinician or a caregiver. How do you quantify the caregiver characteristics?
The content perhaps of communication around an acute pain presentation that I think are impactful, and knowing some of that data would help us modify our treatment systems. Is there a way to measure, perhaps, caregiver gestalt about prognosis for outcome, or is there a way to measure degree of

Page 314

certainty or confidence in the outcome that a caregiver might have? And use that information then to feed back to the system to modify where there might be improvements.
I'm impressed there's some literature in the emergency department that looks at the content of communication and how little we know about that content of communication, and how powerful it could be. As a clinician, that's appealing to me, but I'm not sure how practical or feasible it might be to capture it.
DR. CARR: Maybe that could be environment of care. So it could still go into one of those categories.
DR. TIGHE: I think more broadly that also points to the access of the patient to certain treatment modalities depending upon the healthcare setting, and that is going to influence the experience that you aggregate within this domain.
If certain therapies just were not available or were not culturally used in that healthcare setting, would you consider that in a broader

Page 315

environment or would you have a special subheading for healthcare setting?
DR. CARR: Maybe if there is a difference, I don't know, but maybe change environment to milieu.
DR. TODD: But it would be interesting to see it captured in some sense, whatever bucket it's put in.
MALE SPEAKER: Just for the sake of parsimony, event might be tucked in under core criteria. So for example, post-operative pain, the core criteria is that it occurs within 72 hours of an -- I'm just making this up.
DR. CARR: Good point.
FEMALE SPEAKER: And then 2 and 4 could those be combined?
DR. BRUEHL: The more we combine the better because seven is unwieldly.
FEMALE SPEAKER: Two and 4 together, you mean?
MALE SPEAKER: That could just be one of the criteria that [inaudible – off mic].
DR. BRUEHL: Okay. So that takes this off.

Page 316

Sorry, 2 and 4 you're thinking, risk factors.
FEMALE SPEAKER: Most of the risk factors are sort of applicable to the host [inaudible – off mic].
DR. BRUEHL: They would be characteristics of the host. Yes, that would make sense. So host patient, to me, for lack of a better way to think about it, it's kind of like if I draw a circle around the patient, it's everything inside that; except for pathophysiology because we've broken it out..
DR. DWORKIN: So I was thinking about exactly that, Steve. So host is the moment before the event, and pathophysiology occurs right -- starts right after the event.
DR. BRUEHL: Right after. Okay.
DR. DWORKIN: So host is right at the event, and pathophysiology is after.
DR. BRUEHL: And risk factors were present at the time of the event, so it would make sense to combine that.
DR. DWORKIN: So they're host.

Page 317

DR. BRUEHL: Yes.
DR. DWORKIN: Exactly.
MALE SPEAKER: And then, Bob, let's say two folks get in an automobile collision, and one person -- they have the same -- we'll just hypothetically, the same level of pain. One is way less active because of that pain, really markedly drops their activity.
Is that part of pathophysiology because it's occurring after? You know what I'm saying, in terms of, let's say, just behavioral response.
DR. DWORKIN: So to me I think that's something different. I think that's kind of impact, but functional impact.
MALE SPEAKER: Okay. [inaudible - off mic]. I think impact is fine. Yes, it works.
DR. DWORKIN: Though, I think a lot of us believe that the kind of functional consequences could exacerbate the pathophysiology and that those 2 dimensions could be in a loop.
MALE SPEAKER: [Inaudible - off mic]. I guess in this time frame maybe we could just say

Page 318

impact.
FEMALE SPEAKER: We lost our temporal element. [Inaudible - off mic].
DR. BRUEHL: That goes last. It goes last because that's the only place I have to put it unless it fits --
(Laughter.)
MALE SPEAKER: The only thing I'll say about temporal is it doesn't imply a longitudinal evaluation, and so often we're making these diagnoses cross-sectionally. So we may or may not be in a position to -- like if I'm in the emergency department and it's two hours after something, I may say, oh, I'm going to diagnosis him with this, I'm going to trial this medicine or new intervention. But I don't really know over that two hours has it been temporally or --
DR. BRUEHL: Well that gets at a little confusion I have about the concept. So the temporal, the way we talked about it earlier, to some extent was talking about for a given disorder what was the evidence on risk for chronification

Page 319

and maybe the factors that would be relevant to chronification. So it had to do not necessarily with a snapshot of where they were in the temporal course necessarily, or maybe not just that, but also going forward what was likely to happen.
Now, was I misunderstanding that or is that --
DR. TIGHE: So I would interpret it to mean the anticipated temporal features.
DR. BRUEHL: Anticipated.
DR. TIGHE: How long will this hurt? How long am I going to be at a decreased level of functioning?
DR. RAJA: I think it relates to the pathophysiology. For example, a temporal cause after an amputation in terms of pain would be very different from a skin incision. So there is a relationship between the pathophysiology and the temporal cause.
DR. BRUEHL: Which also relates to the severity of the event, right.
Deb?

Page 320

MS. GORDON: Yeah. No, I'm kind of mixing up in my mind, too, the temporal and kind of the nociceptive burden. If you have a procedure, so I mean there's a liver biopsy, that's very different than a laparoscopic liver procedure versus an open liver procedure. So it's tissue trauma and the time of the event, and I don't know how to fit them.
DR. BRUEHL: But that's part of the event characteristics. We haven't moved this over there, but the locations, organ system, tissue, all can be used to index the degree or extent. And I think that all kind of fell under part of the event if we're doing it the way we'd originally talked about.
Yeah?
DR. CARR: So the temporal component has been mentioned. Are there other characteristics of the pain itself that are part of -- you know, the sensory qualities of the pain? And this is a different temporal feature, but fluctuations in pain; the kind of bodily extent of the pain, is

Page 321

that incorporated?
DR. BRUEHL: It's not. On our list over here, we had pain qualities. Temporal could be considered a quality unless we're talking about the predictive risk issue, where it's not really a -- well, it's kind of a different -- it seems to me like a different thing.
MALE SPEAKER: I think it serves a dual purpose. I mean, it serves a classification purpose and a diagnostic purpose, like you said. So moving away from a diagnosis where I had procedure what pain's going to look like, you think about right upper-quadrant pain, left lower-quadrant pain, ruptured AAA. Those have very distinct temporal characteristics before they show up to the ER, but their management and trajectory -- and that aids in the diagnosis, but their trajectories afterwards and how it is characterized goes into classifying future risk.
So I think it serves a dual purpose. I don't like making things more complicated. My preference, we put it in core criteria, but it

Page 322

might just apply to two different dimensions.
DR. BRUEHL: To put the temporal under core criteria or the risk?
MALE SPEAKER: The diagnostic component of the temporal I think is a core criteria. If you're talking about in terms of risk and classifying for chronic pain, I think an argument could be made to put it into another dimension, modulating factor, pathophysiology.
MALE SPEAKER: Sorry. Go ahead, Deb.
MS. GORDON: Well, I'm just thinking there's another aspect with the temporal stuff, kind of like Brett was talking about with that rib fracture. When you see somebody who comes in with a fresh chest trauma, they look very different than they do two or three days later when that injury blossoms and then they have to get reintubated. So I don't know how that fits in there, but I do think that you go through different phases.
MALE SPEAKER: I'm wondering whether or not it might be better to not have this host as the moment before, again, just to sort of throw out

Page 323

ideas. Because you could say, well, let's say how I respond -- Roger and I are both in a car accident together. He thinks he's going to be fine tomorrow, and I think, oh, my life's over. I'm never going to recover from this, I'm never going to get better, I'm catastrophizing.
So is that, yes, it has a lot to do with how we were the moment before, but it really has to do with characteristics of what our presentation is like? So maybe if we were just like, you know -- characteristics or something that would describe characteristics, but it wouldn't so much distinguish the pre-event or the post-event. I don't know if that's --
DR. BRUEHL: That was really only to try to explain why pathophysiology was separate, which I don't -- instead of calling it pathophysiology, talk about putative mechanisms or something, then we kind of avoid that issue just by relabeling it. And then we don't have to necessarily say.
Because I agree. Catastrophizing three days after an injury, you have no idea what they were

Page 324

doing before or at the time of the injury, but if they're catastrophizing three days later, clearly that is an important thing to know in terms of --
(Crosstalk.)
MALE SPEAKER: These modulators -- these risk stratification things, I'm trying to think what category they'll go in.
DR. BRUEHL: Yes?
FEMALE SPEAKER: What Henrik was saying before is like for some cases, like when you are trying to do research, you do want to know about the pre-operative or pre-event risk factors. So what if we just didn't specify a time and we kept it really general?
DR. TIGHE: So one point that Trip had brought earlier that I think is apropos to this discussion, he had talked about the polytrauma patient, multiple sources of pain.
One of the trends recently in looking at temporal dynamics of pain, also in the broader temporal dynamics of anything, is to consider there's a spatial temporal issue. So we're not

Page 325

looking just at changes over time, but changes in location as well.

I think that's especially apropos again to the polytrauma patient where you may have differential rates of recovery of different types of tissue injury. You may also have continued evolution on a patchy framework.

I think it's very hard to characterize today, but I think as time goes on, that will allow us access to a broader source of information. It may simply be pain radiation patterns, but it could also be differential qualities of recovery over time at different locations.

DR. BRUEHL: So the Dimension 3 that was up here a minute ago said pain quality to start with, temporal may be there. Spatial we're adding. But those all seem to fall under the same category to some degree.

There are different levels of temporality. One is, is the patient's pain worse in the morning? Is it pulsatile? Does it ever remit? Is it constant high? Is it constant low? I mean, there

Page 326

are all these different patterns that may be relevant, may not, I don't know.

Then we've got the temporal prediction issue saying what is the risk for the future? To me, that aspect of the temporality seems to fit under the risk discussion in Dimension 2, but I'm just throwing that out there to see what people think.

MALE SPEAKER: [Inaudible - off mic]. Where is catastrophizing and expectations and all?

DR. BRUEHL: That's under host. I'm thinking of that as all inside that circle around the patient.

MALE SPEAKER: [Inaudible - off mic]?

DR. BRUEHL: No, we've gotten rid of the timing issue on that.

MALE SPEAKER: I made a list a couple months ago that when I would see a patient, I go back in the history and see what happened in the past, and now I have to get involved with this patient. I'm going to read you the list that I made.

History of pain, history of pain medication, history of drug dependence. I said Cures because

Page 327

in California we have Cures. It's a program that we go look at the drug history of the patient.

History of anxiety and depression. History of chemo. I mean, patients with chemo, oftentimes they come, they have severe pain compared to the same. Pain with previous surgeries. Duration from the last surgery.

I mean, if you had a surgery a month ago and now coming for the second surgery, the pain definitely out of control or most of the time. Allergy to pain medication. Side effects from pain medication. This actually defined that person or host.

Pain out of the surgical site. If they have a surgery and they're complaining of neck pain, shoulder pain, or back pain or something. Barriers, like extreme age, psychiatric illness, or neurological disorder, culture differences. And emergency surgery is another one that oftentimes we deal with the uncontrolled pain.

So these are lists that may be helpful.

DR. BRUEHL: It sounded like not all, but

Page 328

most of those could be categorized under these labels that we had before. What we need to do is take some of these broad categories we initially came up with and make sure they all fit under something here.

Just so I don't forget, I'm going to go ahead and stick under Dimension 2 the chronicity risk. We can move it later, but I just want to make sure that that's still a point that's kind of not absolutely clear.

All right. So what that leaves us with is, let's see, 3, 4, 5, so we have 6 dimensions, if I counted right. All right.

FEMALE SPEAKER: [Inaudible - off mic].

DR. BRUEHL: Maybe, yes. Yes?

MALE SPEAKER: Where is temporality?

MALE SPEAKER: Still thinking about the AAPT interventions. Where do common features appear here? Because, for example, that would be an area where one could report response to pain treatments or pain medication. Is there a common features in this?

Page 329

DR. BRUEHL: There is not, and that is an option is we --
MALE SPEAKER: Why?
DR. BRUEHL: -- we can call it common features and re-categorize things as that, if it makes sense. So as it stands now, in case you can't read it -- and I'm just going to make a note here about the common features.
All right. So what we're got is core criteria plus the event, characteristics of the event. So this would be what you would use as your primary way of determining does the patient have this condition, is just following your Chinese menu thing up here for Dimension 1.
Dimension 2 is risk factors, host, patient internal, just anything in the circle around that patient, which might include the risk for chronicity as well.
Dimension 3 is pain qualities, spatial qualities, temporal characteristics, timing maybe with regards to the event, that kind of thing. And that's something I guess we didn't specifically

Page 330

talk about, but how long it's been since the surgery, and when you're doing the evaluation and diagnosing that's probably relevant.
Dimension 4 is environment. I'm not entirely sure what we mean by that. I mean, I can certainly see some of these things like the legal and work related issues, family, all that.
MALE SPEAKER: [Inaudible - off mic].
DR. BRUEHL: Environmental context.
DR. CARR: And milieu of care.
DR. BRUEHL: But is this the external? Because we've already got the host here, which is kind of the internal environment. Is this the external environment context?
FEMALE SPEAKER: Yes.
DR. BRUEHL: Okay. Probably not a good label for it, but we'll --
DR. CARR: So we have milieu of care.
DR. BRUEHL: Should I write that down, Dan?
DR. CARR: Yes, I mean I thought that Knox made a very good point to that --
DR. BRUEHL: Milieu.

Page 331

DR. CARR: -- what's this interaction, what's the social thing?
DR. BRUEHL: Plus it sounds very fancy, so I like it.
DR. CARR: Yes, we love it.
(Laughter.)
DR. CARR: One other comment is just that we have the world's authorities on the whole series of impact to publications, but we also have Paul who first authored a great recent paper on acute pain trials.
So there may be some role to kind of thinking about what did that review of acute pain trials show, and could it be mapped onto this system. In other words, is there some gap that we're not thinking of or how does it fit together with the literature.
MALE SPEAKER: [Inaudible - off mic].
DR. BRUEHL: I'm sorry, somebody else had their hand up first.
MALE SPEAKER: Oh, that's fine. Hi, Mark. What about functional consequences? It's been --

Page 332

DR. BRUEHL: Impact.
MALE SPEAKER: That's the impact?
DR. BRUEHL: Yes.
MALE SPEAKER: Because --
DR. BRUEHL: So I should clarify that.
MALE SPEAKER: Yes, because you could tie that to many of these topics that we've talked -- you know, specifically what's the functional impact of the psych issue, the opioid tolerance, the prior history of chronic pain?
It seems that often those are discussed in a clinical context, one after the other, and can have a -- direct care, that's really important. Thank you.
DR. BRUEHL: Rosemary?
DR. POLOMANO: So again, some of these fit into some common buckets. So for the risk factors, the biological or getting the precision science in there with genomics, psychological, social, and environmental. And also for punitive mechanisms, I like that better than pathophysiology because acute pain isn't always pathologic. I mean, right? It's

Page 333

not.
I like the punitive mechanisms because you can use the same thinking because it's not really just biological mechanisms. There are punitive mechanisms. PTSD I think is a punitive mechanism. And that might be a risk factor for pain, but it's also a sustainer or -- so again, in category 5, those same buckets of biological, psychological, social, and environmental might hold true.
I'm thinking we had talked, and Mark had mentioned, about education, because I really think Dan and I just got done doing an evaluation of the medical licensing exam, the USMLE, and we'll have a publication coming out soon. But it was woefully or dreadfully disappointing in terms of the amount of questions and competencies.
I'm just wondering if we think a little farther. We've got research that we're thinking about. We've got practice. And we think about education, and we think about the competencies. And I think the big competency is the nature of pain, the core competency, the coming out with the

Page 334

nature of pain coming out in here, which would be 5, and to kind of cross-link that. And then the assessment of pain competency, which really falls into 2 and 4. So to just not lose track of the educational competencies that we've defined.
DR. BRUEHL: Yes, that's a good point.
I'm sorry. Brett, you've had a question for a while, right?
DR. STACEY: Yes, this is pretty brief but --
DR. TURK: This is the last question.
DR. BRUEHL: What?
DR. TURK: Last question.
DR. BRUEHL: You're sure? Two, that's it. We'll get to you two, and that's it.
DR. STACEY: My thing is about trajectory. People on post-op day 2 who have expected amount of pain after an event are quite different than people 10 days out, who, as Henrik pointed out, the group that have recovered have minimal pain if they kind of overdo it versus the people for now whom pain is quite different.

Page 335

It's almost a different thing. They have the same insult, the same injury, the same initial start, but were on the wrong trajectory. Those are different. I don't know how you kind of say here's an expected trajectory, here's someone who is off. Somewhere you have to look at healing and expectations.
Is it all just three? Is that just that?
DR. BRUEHL: I would think that would fall under the temporal because you're always going to be judging whether it's appropriate pain or not by how long out it's been from the injury and --
DR. STACEY: So we use the same diagnosis on post-op day 2 and on post-op day 25?
DR. BRUEHL: That would depend on whether they meet the core criteria. And they could all meet the core criteria. That is, they fall in the bucket, but be qualitatively very different in the specifics, and that's what's captured here, hopefully, if we've done our job right. But I'll add trajectory here to Dimension 3 just to make sure somehow we address that.

Page 336

DR. TIGHE: It would also pertain to the context of the events at the time. So somebody who is in 10 out of 10 pain but doing their ninth lap, that's a different event than somebody's 10 out 10 pain lying still in bed. So the context is key there as well.
DR. BRUEHL: Okay. And we've got one more.
MALE SPEAKER: Sure. I'm still just trying to rectify event in my head for this specific reason. If I have right upper-quadrant pain, is acute visceral right upper-quadrant pain the event, or is acute cholangitis the event? Or is the inflammation of my hepatobiliary system leading to pain signaling the event versus I just broke my ankle? Is the event I just broke my ankle, or is the event that the bone's broken and the inherent macromechanisms that are associated with that?
I think this might be -- and I think this is probably the answer -- maybe not the answer, but a lot of good discussion tomorrow where we have processes such as acute post-procedural pain, I know what happened, versus orofacial pain, which

Page 337

can be a fracture, an abscess, some other syndrome. Acute visceral pain, it could probably be 500 different diagnoses.

So in my mind going in tomorrow I'm struggling with event, so hopefully I will work it out tonight.

DR. BRUEHL: Well, and I think event was a short -- if I recall correctly, now, event was a shorthand way, in a sense, of also getting at the extent of the tissue trauma.

MALE SPEAKER: [Inaudible - off mic]. Well in the context lots of things. But it doesn't -- event's under core criteria, and it doesn't always have to be present. You know, there may be certain types of pain for which there is no event.

DR. BRUEHL: That's true.

MALE SPEAKER: But for certain times, it's a sine qua non.

DR. CARR: Can I just as a comment, I'm actually optimistic about that because I'm thinking back to you know being taught how to do history in

Page 338

physical, and when you write it up and hand it in to your preceptor, there's a part called history of present illness. And, generally, people get that right. You don't wind up giving the history of an irrelevant illness. I'm optimistic that that can be dealt with, but it's a good point.

MALE SPEAKER: All right, that will do it.

DR. RAJA: [Inaudible - off mic].

DR. BRUEHL: Yes, right. Yes, onset very broadly -- I'm just going to put that in quotes. It could be all kinds of things. All right. I guess that's it, right, for now.

MALE SPEAKER: [Inaudible - off mic].

DR. BRUEHL: Yes, we will. Yes. I know the cartoon you're referring to.

(Laughter.)

MALE SPEAKER: Could you please restate the homework.

DR. BRUEHL: Think about these things. Come up with a solution. Be brilliant tomorrow.

(Whereupon, at 4:51 p.m., the meeting was adjourned.)

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