ACTTION-APS

Pain Taxonomy Meeting

July 19, 2014

A Matter of Record

(301) 890-4188

ACTTION-APS PAIN TAXONOMY MEETING

Saturday, July 19, 2014
1:05 p.m. to 3:57 p.m.

Westin Annapolis
Annapolis, Maryland

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

(1:05 p.m.)

DR. BRUEHL: Let's go on and get started. We're on a little bit of a tight time schedule this afternoon because obviously a number of people are leaving. And unlike what is on the agenda, we're going to try to shut things down by 4:00, regardless of whether we've finished or not.

Now, just keep in mind here to keep on schedule because the number of groups we've got -- Bob had this all worked out. So we've got about 15 minutes total for each working group to handle what they need to handle. So what we would like to do is have discussion that is no more than 10 minutes. And then the remainder of that time, up to the 15-minute mark, is discussion and questions and that kind of thing.

I'm going to be actually timing just to keep us on track. And I think if we have questions that are urgent that we need to get addressed, why don't we write them down. And then maybe after the meeting is over, we can discuss them more, those of

Page 5

us that are still around, kind of come back to those.

Presumably, every working group has a presentation of some kind, maybe PowerPoint or some other program. The computer up here is ready.

Has everybody loaded what they want to display during their talks? No? Okay. If you want to get a thumb drive, you can just put it directly on there, and we'll be okay.

So when you were up here -- the way it was written was that there were going to be multiple people. So like the working group co-chairs would be presenting this potentially. Because there might be more than one person, we had it set up so that you could just sit up here. Whoever is going to be doing this can talk. Please use the microphones so this can get on the transcript. We've got the clicker up here for advancing the slides, and you can see the slides from the front. So this should work okay.

Now, we're going to start -- the questions about -- thank you. Say your names, please, when

Page 6

you start -- if you bring up questions of anything when you start talking. I'll try to introduce each group so that gets on the record who it is that's presenting.

The first group is going to be the Neuropathic Pain working group, and this is -- Roy Freeman and Rob Edwards were the co-chairs. And it's for the central pain. So we've got peripheral and central are two separate issues.

Presentation - Roy Freeman

DR. FREEMAN: My name's Roy Freeman. We decided that we would combine the central and peripheral group, and the entire group had some heavy hitters. Stephen was part of the group. Bob Dworkin was part of the group. Simon was part of the group, and you see the three over here. And each one of the group brought three opinions to every topic we discussed.

(Laughter.)

DR. FREEMAN: I've decided to ignore most of those. And so what you're going to hear today, now, in the next five minutes, is going to be kind

Page 7

of brief, a distillate of all of that. But don't be too surprised if Bob Dworkin says, "That is not what I said."

(Laughter.)

DR. FREEMAN: And when he does that, just ignore him.

Okay. So here we go. We were the central and peripheral neuropathic pain group. We decided to combine the two groups together and to come up with an approach that was concordant with the diseases that were within both set of charges that we were given.

These are the disorders: central post-stroke pain; spinal cord injury pain; pain associated with MS and peripheral DPN; idiopathic peripheral neuropathy; post-traumatic neuropathy, including that induced by surgery; complex regional pain syndrome; and PHN.

Now, in putting this together -- and we are going to focus purely on Dimension 1 -- we negotiated our way between and wanted to provide some value added to what was put out by the IASP,

Page 8

the two articles by Rolf-Detlef Treede and Troels Jensen, and also position papers that have been taken by various diabetic peripheral neuropathy groups. So what we hope, particularly in the peripheral side of things, is that we would provide some value added to that.

So these are the proposed core diagnostic criteria. I mentioned one that would fall in the basis of the diagnosis. And we showed as the first criterion to focus on history. It's going to look as if this was a no-brainer, but I would say a good hour was spent discussing where history should be in these criteria -- so a disease that affects the somatosensory central or peripheral nervous system; for example, spinal cord injury, stroke, MS, diabetes, chemotherapy, trauma, surgery, and herpes zoster shingles.

Now, the challenge was, at least for the peripheral people, that in 50 percent of peripheral neuropathies, generalized peripheral neuropathies that look, to all intents and purposes, like HIV and DPN and all of the other causes of a peripheral

Page 9

neuropathy, no cause is found.
This is a challenge. And the way we chose to deal with this was that these would be the building blocks upon which the classification was built and would apply to a greater or lesser extent, and most times to a greater extent to the various disorders that were subsumed under these specific core diagnostic criteria. So this is Criterion 1.
Then we said that pain for at least three months -- and there was some debate as to the duration -- that confirms to a recognized neuroanatomical distribution of a simple nervous system lesion or one or more cranial nerves, peripheral nerves, or nerve roots.
I appreciate, with respect to the nerve roots, that there's going to be some overlap with John Markman and his group looking at spinal and low back pain. But certainly, radiculopathies are midway between the peripheral nervous system and the central nervous system. So we felt it had to include that just in the interest of completeness,

Page 10

not to leave a void between the central and peripheral nervous system and look at pain over that. We'll come back to that in a second.
There also needed to be positive signs -- for example, allodynia, hyperalgesia -- and/or negative signs -- sensory loss and/or weakness -- that conforms to the distribution of either a central nervous system lesion, one or more cranial nerves, peripheral nerves, or nerve roots. So we've got a combination. We've got a history. We've got symptoms, and we've got signs.
Then -- and this is the challenge. And this is the missing piece on all of the attempts to come up with -- various organizations -- how many and what positive signs and what positive symptoms using what questionnaire are necessary to make the diagnosis. And we proposed, our best guess, that one of each was sufficient, but we do not know that. And nobody knows that. And surprisingly nobody knows that, and this is part of our research agenda.

Page 11

Then we thought -- and here was another one of the challenges that we faced -- what about the general practitioner operating in an environment where he doesn't have access to the special investigations? So we added, when possible to confirmation of a lesion by objective tests; for example, neuroimaging for the central guys, neurophysiology for the peripheral people or perhaps for the central people, and pathology, and in particular, skin biopsy.
Then finally, this specific condition could not be better explained by anything else.
There were issues, which we barely touched on, on how to deal -- when we specify a particular territory. And I don't have time to go into the topographical approach that we proposed to this, how to deal with referred pain, very common, for example, in entrapment neuropathies such as carpal tunnel syndrome, extending beyond the innervation territory; how to deal with extension outside the innervation territory due to central sensitization.
These are the challenges with any such

Page 12

taxonomy. And also, we did not define specifically the temporal relationship to the toxin, the insult, the infection, or the injury.
Research agenda we thought would be divided into stages. The first stage, we would make use of a number of existing databases in which signs exist and symptoms exist. And there are a number of databases using pain detect, the NPSI, various other symptom infantries.
Also, using quantitative sensory testing, both bedsides, easily performed at the bedside, and more complex using sophisticated instruments, we would use these to look at what combinations, what patterns of signs and symptoms, were necessary to specify a diagnosis. And we would use the -- let's call it the Steve approach, stage 1, that he had with CRPS to try and look for patterns that would actually give an evidence-based numeric basis to the one or other sign or symptom that we proposed for criterion number 2 and 3.
Then -- and this is still under discussion -- we proposed a more extensive study in

Page 13

which we would pick one or two of our disorders, and we would prospectively, using prespecified symptoms and signs, define what are the ideal combinations. And in that situation, we would have a prespecified comparator disease.

For example, for diabetic or any other peripheral neuropathy in which there is foot pain, we would have as a comparator plantar fasciitis. And this is all topics for additional discussion.

I think that summarizes -- that I think is a reasonable summary of what we discussed over the past two days. I don't know if Rob and Eva want to add anything.

We are open for questions.

(No response.)

DR. BRUEHL: Somebody must have a question.

DR. FREEMAN: Just to make us feel that this was not all in vain.

(Laughter.)

DR. BRUEHL: We're in such awe.

DR. FREEMAN: Let's get out of here.

DR. BRUEHL: Before they pin you down on

Page 14

tough questions, right?

I do think that the research agenda part of this -- when we came up with this -- well, let me back up. For the CRPS, there were a multitude of features to look at, the edema, color, temperature, range of motion, all these things. And when we came down -- I'm just being honest here with what happened.

When we came down to looking at this, really, there's that one area in our diagnostic criteria where we've got a positive and a negative sign or symptom, and that was it. We couldn't even come up with exactly what those should be, some things like allodynia, some numbness, sensory testing that indicated numbness, that kind of thing.

So what we were trying to do, though, is look at the literature and what prior diagnostic criteria had suggested as features to look at and diagnosing it. And those were the positive and negative things we were considering. But we also wanted to go a little broader than that and

Page 15

consider looking at the neuropathic pain questionnaires that have a lot of descriptors of pain to see, for example, whether maybe burning pain is something that is common enough in most people that would have this diagnosis, that would actually be useful in diagnosis. But we weren't sure it was.

That's the kind of thing we're leaving open to empirical testing later on and hopefully would be able to find away to justify whether that needs or doesn't need to be included in there.

Yes?

DR. WESSELMANN: This is Ursula Wesselmann from the German Neuropathic Pain Network, which is such a long testing paradigm, which as you said is not possible really to do in mass settings. But has anything filtered out to be more useful than the other one to phenotype?

DR. FREEMAN: So let me answer you. I want to just elaborate -- you get a taste of what our group was like -- on something that Steve said. And that is, I think in designing our clinical

Page 16

trials, we also want to be very careful -- in designing our research studies, we want to be very careful of the circularity that is a huge part of all of these kind of research studies in which best available clinician diagnosis is that burning pain represents small fiber neuropathy. So the gold standard is burning, and the conclusion is burning is the core feature of peripheral neuropathy.

You can look at all of these studies and bang your head against the wall. So I think in designing this -- and we discussed this in some detail. And why I said more to come is that we want to try and do a study of that nature and avoid the circularity, but it's not so simple.

So that's the one point. Then the other point about the German network, the German network doesn't really address this question. It brings in patients that have specific disorders and they look at the pattern. It doesn't go backwards, which is the way we want to do. That's one thing.

The other is that I put together a very short evoked pain, quantitative sensory testing

Page 17

assessment, which can be done at the bedside using tools from Home Depot, and can be done in 15-20 minutes. And Pfizer actually has used this to make clinical trials, and we've reported in Pain last year.

So there is a potential tool available that can be used in 20 minutes, which will use -- von Frey has -- a series of evoked pain assessments, including temporal summation, and can be done at the bedside. So there is something available to do something prospectively.

DR. BRUEHL: So we were trying to factor in the bedside issue versus requiring a lot of fancy testing, and we tried to fudge that by the wording about "if possible" the confirmation by objective test.

In the circularity issue, just to reiterate because this will be across all groups -- so the options we have are something like Roy just proposed up here, which is looking at a database of signs, symptoms, test results, and looking at frequencies, correspondence between things. You

Page 18

can use factor analysis, cluster analysis, to try to identify patterns in those things that hang together; things that overlap and may be redundant. So those kinds of questions.

We've got the sensitivity/specificity issue in the -- honestly, these are like bootstrapped research studies because there is a circular argument in them. But in essence, what we can do is we can take our criteria that we come up with that we want to test, and then we've got a comparison group that we have to diagnose somehow.

But let's say that we just have some clinician agreed upon this is what the other condition is. And then we use those criteria that we used to define the first group to see if we can discriminate between those two groups.

It sounds ridiculous, but it actually can provide some useful information, especially when you talk about what happens if I add an extra requirement for this sign, or that sign, or change this. You can look at relative changes. So that's kind of what we have.

Page 19

The third option we've got, which is problematic but it's a possibility and it provides a bronze standard is clinician agreement. So if we can get expert clinicians who can look at the same package of data and say we both agree that this person has X disorder, then that becomes another source of information for validating the criteria, validating it against clinician opinion, which also may be not very good, but it's another approach.

So all of those approaches can be used for any one of these conditions potentially. I just wanted to say that one time. I won't say it again.

DR. FREEMAN: John, you look like you've got a good question.

DR. FARRAR: Me?

DR. FREEMAN: Yes, you.

DR. FARRAR: John Farrar. I'm hesitant to say this, but I'll say it anyway. What about using prospective testing using drugs that we think have an effect on the mechanism? You're clearly going to be influenced by the fact that there are lots of other reasons why certain people might not respond.

Page 20

But if you took two diverse groups -- if you took a group, and you looked at those who had an outstanding response versus those who had no response, could you use that as a way of bootstrapping, again, to come up with the major issues?

DR. FREEMAN: This came up briefly, and I'm going to defer to Eva to answer this question. It came up briefly in our discussions. And it came up specifically with spinal cord injury pain, where the spinal cord injury pain was mechanical, neuropathic, and mixed. And Eva mentioned that the mechanical responds to non-steroidals and the neuropathic presumably responds to neuropathic drugs.

We didn't discuss this in detail. We let it drop. But I did think about that, and I want to hear what you think about John's suggestion.

DR. WIDERSTROM-NOGA: First, logistically, it's difficult to do, of course. It will take a long time for us to get an appropriate sample size.

One of the issues that we have in spinal

Page 21

cord injury is that people have concomitant -- several types of pain with different mechanistic underpinnings. Some of them are probably overlapping and some of them are different, so it makes it very difficult for us to do it in spinal cord injury.

DR. FARRAR: Could I follow up?

DR. BRUEHL: Let me just let you know. We're at 17 minutes already, so we're over this first one. Some of these questions are kind of going to be things that will apply going forward. That's probably okay. But make sure it's urgent at this point now. Urgent questions? You can bring them up with the next group I'm sure.

(No response.)

DR. BRUEHL: All right. Let's move on to the next one. And again, if there's something that you didn't feel got resolved adequately in this discussion, write it down, bring it up after the meeting, and we can talk about it some more maybe.

So we've got Steve George and John Markman who are going to be covering the spine pain.

Page 22

Presentation - John Markman

DR. MARKMAN: Good afternoon, everyone. This is Steve George, and I'm John Markman. We're from the low back pain group. We just want to give you a window into our deliberations. We have a diverse working group, so we began with a series of exercises just to develop a core, sort of trust, among the group. So we just began our deliberations with this process.

(Laughter - slide shown.)

DR. MARKMAN: We found it very helpful. The reason that was so important because we started talking about back pain, and we had a chiropractor, a psychologist, a physical therapist, a psychiatry expert with a degree in philosophy, a neurosurgeon, and a neurologist all talking about low back pain. So we really need to find a little common ground to start.

I'm going to let Steve talk about Dimension 1, where we tried to address and inoculate against what Roy just talked about with the circularity issue.

Page 23

Presentation - Steven George

DR. GEORGE: Dimension 1, I think, conceptually, one of the things that helped us define Dimension 1 was sensitivity versus specificity. And we took a very sensitive approach to Dimension 1 and really took also a philosophy of this being more purely a taxonomy than a diagnostic criteria because the diagnosis of back pain is not really a major issue right now. I think what may be of more value is that this is, on a scale or on the continuum, much closer to description of syndromes.

So we actually for Dimension 1 -- and it may have been the trust exercises. After that, I think we made some good progress. We felt pretty comfortable with having it be patient self-report of chronic low back pain, used the NIH definition of chronicity to define the temporal part, and then the location is actually part of Dimension 1, where it's in the region between T12 and the gluteal fold. So that's our Dimension 1.

Really, we talked about including signs

Page 24

here, but we really -- there is essentially no sign that we're aware of that can rule us out at this time if someone reports these symptom characteristics. So that was our take on Dimension 1.

DR. MARKMAN: We were also I think trying to address what happened with the NIH low back pain working group --

DR. GEORGE: Yes.

DR. MARKMAN: -- where their attempt to develop a research diagnostic criteria really, as our fight with this, was a bit of a modified effort where they felt they couldn't do that because they didn't start like this. And instead ended up just with a minimal data set. So we wanted to navigate away from those shoals, and that's why we really focused on sensitivity in Dimension 1.

So we had a lot of constructive dialogue between the members of our group, and this was part of an ongoing discussion.

(Laughter - slide shown.)

DR. MARKMAN: And here we have a lot of

Page 25

contemplation as well, which we found very helpful. And then in Dimension 2, we tried to think about how do we now pull up the lever on specificity.

We thought about the different kind of systemic illnesses directly involving the lumbosacral region that we would want to exclude or we'd want to look for if we were [inaudible - intermittent mike] -- file patients out, look at the effects of previous therapies, the lumbosacral spine, whether it's surgery or radiation therapy, or other types of interventional approaches which modify the anatomy. And then, we were also going to look obviously at associated symptoms signs and different diagnostic testing results.

So this is kind of what we decided we were going to make our overview of Dimension 2. And why don't we start with those systemic diseases. Steve?

DR. GEORGE: These are just examples. Frankly, these are what are most commonly used as exclusion criteria in trials for this. But since we had Dimension 1 be so broad, we thought this

Page 26

would give the option of people looking at some of these subsets of people that typically are excluded from the non-specific chronic back pain. And certainly you can still have that option because these can be all yes/no and present or absent, and you can start, as John mentioned, dialing in the specificity.

So we used the APS and the American College of Physicians' clinical guidelines that were published in 2007 as our foundation for looking at which types of systemic illness we would want to be aware of after identifying the general characteristics of back pain. And they're all listed there. I don't think there are any surprises there.

DR. MARKMAN: This is where the discussion got a little bit knottier as we started to think not so much about these therapies, pharmacologic therapies, non-pharmacologic therapies, including a whole range of behavioral and multimodal interventions, as well as, as I mentioned, surgery and radiation therapy.

Page 27

Again, this would be how we might parse different populations that we wanted to look at. And these weren't so much I think looking at necessarily responsiveness to these pharmacologic interventions as really [inaudible - intermittent mike].

Other, as you would expect, associated symptoms with chronic low back pain present for three months within the last six months, that was between T12 on the gluteal fold, we would look at these associated symptoms, the lateralization of the legs or a bilateral presentation, whether it was axial or leg predominant, other sites of pain, weakness, perceived weakness, sensory disturbance and evoked pain. Then there, we're really thinking about syndromes such as neurogenic claudication or patients who have pain, which is evoked by standing and walking.

We discussed looking at different signs, including the ones you would all expect would be typically done on a neurologic exam or any standard primary care exam of chronic low back pain.

Page 28

Impairments here, we broadly talked about things like loss of range of motion.

What we really got stuck on, I think struggled with a little bit, was really how to incorporate -- and myself in particular -- the global assessment of pain behavior within these categories and how do we handle that, so much I think that if we were going to use the bronze standard, as Steve talked about, and look at clinician agreement, I think so much of clinician assessment of chronic low back pain syndrome is informed by what the patient's face looks like when they take off their socks or other pain behaviors of the grimacing and the groaning and the slowed movements.

The question is how do you bake that in to these associated signs that the clinician is observing.

So I don't know that we have an answer for that yet. But I do think that if we were to show videos to five clinicians and ask them to make the diagnosis in the subtyping, we may have a challenge

Page 29

if we don't figure out how to do that.
Again, this is standard diagnostic testing, whether it be differential diagnostic blockade with local anesthetic injections, neurophysiology with EMG or, as you would expect, all the MR and CT and plain film imaging guidance, as well as ultrasound of non-osteo structures.
DR. MARKMAN: Then comorbid conditions that we thought for Dimension 3, and I'll let Steve take it.
DR. GEORGE: Yes, and we can kind of speed through these. And we realized that these may be federal issues, so we just put some down that had some linkage to chronic back pain, mental health substance abuse, osteoarthritis, and obesity. And then this idea of picking up on whether it was isolated chronic low back pain or it involved pain in different areas, we thought were ones that if they're not covered federally, we could cover them specific to back pain.
Consequences are along the same route. I don't know if these are specific back pain or not,

Page 30

but we were just thinking of putting some of these up here. And again, if these end up being federal issues, that's fine. We certainly have our work cut out for us in Dimension 2.
Then these are risk factors that are more or less established in back pain. And again, I don't know if any of these are specific to back pain. There may be a few in there, but, again, these may be federal issues. But we just kind of wanted to get those. I think it helped us hash some things out.
DR. MARKMAN: And then we're sort of talking about the next steps for where we're headed. I think we see our immediate needs as sharpening Dimension 2 as best we can and using that conversation over the next couple months to finalize the data collection form, and then probably working I think next toward a vignette development to look at what these cases might actually look like.
Then maybe go for some preliminary validation along those lines. And then go from

Page 31

there and collect comprehensive data and undergo data reduction, look for empirical derivation of subgroups. And then work toward harmonizing this with some of the other efforts out there like the NIH low back pain, minimal data set, as well as some of the other registries. So that's some of the other work that we saw ahead for our group.
So we'll stop there and just take any questions. Steve, do you have any comments to start?
DR. BRUEHL: I would have actually a question. You notice on the one that we did -- this is Steve Bruehl -- for neuropathic pain, Dimension 1 is the Chinese menu list required for diagnosis. And I notice that you've got a dimension 1 that is extremely brief, and it basically diagnosis back pain.
My question is, are you going to further subcategorize specific diagnostic labels for radicular back pain, and then the associated signs that were listed under Dimension 2 here become part of that menu, Chinese menu, in Dimension 1? How

Page 32

are you planning to do that? Or is there just going to be an overall back pain diagnosis?
DR. MARKMAN: Well, I think this is the challenge. As you know, one of the reasons we wanted to leave the back pain diagnosis as sort of the anchor for all of these is because, on the basis of prevalence, it's 95 or 90 percent of the cases, and it's so often non-specific. So we wanted to honor that fundamental observation that everyone shares.
I think what we felt the risk was of moving those things up to the first category, or exactly what Roy was talking about, that if we a priori say that having a disc herniation is important or having radicular syndrome is important, we're going to foreclose on the journey of empirically validating this. We're just going to be basically codifying the received wisdom.
I think that to the extent that that's what we're doing, why are we doing it, really? We're obviously not going to -- unless that's what we're really just trying to do, is put the imprimatur of

Page 33

this group on what's already been done, I think we're going to get stuck if we do that. I think we have to start with the fact that [inaudible - intermittent mike].

DR. MACFARLANE: Gary Macfarlane from the University of Aberdeen. I'm just thinking of using these in epidemiological studies, and I'm thinking that in Dimension 1, someone could be positive for that, even though they do not currently have low back pain. Dimension 1, is it a part of chronic low back pain, which is described as more than three months from the past six. So people could still be positive for that even though they're not reporting.

DR. MARKMAN: In the actual interview.

DR. MACFARLANE: I'm just --

DR. MARKMAN: Absolutely. Obviously, we have this problem, patients with lumbar stenosis will be sitting in front of you and be pain-free, and only when they get up to walk will they be symptomatic. So again, it's an analogous situation on the minute-to-minute basis, let alone on the

Page 34

month-to-month or the year-to-year.

DR. MACFARLANE: But I just wonder whether in Dimension 1 you want to have some measure of current low back pain because I can just see us in larger research studies misclassifying people as having chronic low back pain who actually may have recovered. And it's just a challenge of having to use these in different settings.

DR. MARKMAN: So maybe we can work on that, and I'll bring that to our group about somehow integrating the idea of present pain intensity.

Sam?

DR. S. DWORKIN: Hi. This is Sam Dworkin. The research task force of the pain consortium that I referred to took exactly the same tact that you are taking, with some differences in Dimension 1 that I'll mention in a minute; that is to relegate all of those putative diagnostic categories of chronic pain to the research agenda because they, too, could not come up with diagnostic -- reliable and valid criteria for back pain.

But there were two exceptions that I

Page 35

wondered if you deliberately excluded or just failed to discuss. One was the addition to the definition of chronic pain, which was six months, I believe. But that part's not so important. But it also included to address the issue just raised, was that it was present on at least three days of -- it had -- I can't remember exactly, and I don't know whether Dennis or Partap remembers exactly.

So it's pain over, say, three months, pain present on at least three days in the last three months or three days out of a week or something.

DR. TURK: They included that. They had 30 days of pain within six months, which would basically be you have to have it --

DR. S. DWORKIN: But the task force included it.

DR. TURK: No, theirs said so.

DR. S. DWORKIN: Oh, I didn't see that. I didn't hear about it.

DR. KHALSA: This group, the working group, essentially adopted precisely the definition that the task force recommended.

Page 36

DR. S. DWORKIN: Oh. I'm sorry. I missed that. Congratulations.

DR. KHALSA: So chronic is defined as greater than three months within the last six months. So it's the idea that within a six-month time period, someone could have pain every other week, that kind of thing.

DR. S. DWORKIN: Okay. Then the other thing that I didn't hear you say was that the task force further extended the definition to include an assessment of the impact of pain, and again, with good evidence for doing that, and wondered whether you had considered that as part of the definition or rejected it and had reason for rejecting it.

But that's in the NIH report. It's both on the website of the NIH Pain Consortium and in articles that have appeared in the Journal of Pain, the clinical Journal of Pain, and other journals, the report describing the products of this research task force on standards for research in back pain.

DR. MARKMAN: So I just want to make sure I understand. In Criteria 1, you would have a

Page 37

functional impact write-up in Dimension 1?
DR. S. DWORKIN: Yes.
DR. MARKMAN: Okay. John? And then we'll stop, I guess.
DR. FARRAR: John Farrar. I think an issue that might affect the way this is done, it seems to me at the end of the day, a person who comes in and says my back hurts, their back hurts. And so I'm not at all sure that we need to validate this with regards to whether or not they're malingering, which I think is sort of the only other alternative.
Your fourth bullet on your research agenda was to come up with subgroups. And I would argue that the biggest issue in this process is whether the pain is predominantly neuropathic: local inflammatory, a mix because you've got discs that's pressing on nerve, et cetera. It obviously overlaps with the neuropathic pain group. But I would prompt or suggest that a major focus be on looking at those issues. And there should be data sets out there that would perhaps help you with

Page 38

that, that I'm happy to talk about more.
DR. MARKMAN: Just so I understand. If you're going to try and create a nociceptive versus neuropathic dichotomy, where would that fit into the dimensional structure of this? Would that be a sign, a symptom, or that would be a separate access along Dimension 2, would be neuropathic versus nociceptive?
DR. FARRAR: I would argue that back pain is a category of syndromes and that you need to define each syndrome separately within that. And you would come up with criteria so if I wanted to look for predominantly neuropathic back pain, I would choose this set of symptoms, this set of signs, this set of issues. And if I wanted to look at predominantly muscle-related pain, I would choose this set of symptoms, this set of signs with these issues.
DR. KHALSA: So we did discuss that actually at some length. I think the paradigm that the working group adopted here was the idea that within Dimension 2, you would have -- you're essentially

Page 39

building this matrix of all these different aspects, including signs and symptoms.
Without prejudging it -- and this was the challenge of we don't want to just sort of jump in and say, well, everyone knows what a disc herniation is. It consists of this and this and this. But rather develop the whole matrix, and then apply research to essentially be able to, can we in fact validate that these constellations of things result in what we call discogenic back pain and that kind of thing.
DR. BRUEHL: We're kind of out of time here. I would like to point out one thing, just usability of this. If this were to get published and becomes clinically usable, it would probably end up being like DSM has used for psychiatric disorders, where what you'd see on a report or something is the diagnostic code for Axis I.
So just keep in mind that if all Axis I is, is it says this person has chronic back pain, that is going to be the diagnosis that patient will carry on the clinical report, and there may not be

Page 40

room to put all the Axis II information.
I think that was a little bit, John, what you're getting at. That was kind of where my question was coming from. I agree with you completely that not prejudging what the mechanisms are makes a lot of sense. But at some point after reviewing all the Axis II information with research, would there be a plan to move towards separate subcategories for these different types of pain.
DR. FARRAR: And doing that with a table makes absolute sense. But I completely agree with you. It needs to be 179.1, 2, 3, 4, 5, 6, 7, which defines different kinds of back pain.
DR. BRUEHL: Right. Okay. Can we move on?
Next, we have Fibromyalgia and Chronic Myofascial and Widespread Pain. We've got co-chairs Lesley Arnold, Robert Bennett, and Leslie Crofford
Presentation - Leslie Crofford
DR. CROFFORD: As Lesley Arnold is pulling that up, I'd like to thank everybody who was here

Page 41

and participating. I'm Lesley Crofford. We had a very wonderful international group. We had Dan Buskila from Israel, Dan Clauw from Michigan.

DR. BRUEHL: Excuse me. Everybody who's speaking, speak into the microphone.

DR. CROFFORD: I'm lighting up. Can you hear me? Okay.

So Dan Buskila from Israel; Dan Clauw from Michigan; Jan Dommerholt, who was our myofascial pain representative from Bethesda; Mary-Ann Fitzcharles from Montreal; Gary Macfarlane from Aberdeen, Scotland; Li Alemo Munters from Sweden; Eduardo Paiva from Brazil; Piercarlo Sarzi-Puttini from Italy; and Roland Staud from Florida. So I'd like to thank everybody for participating in our little group.

Presentation - Lesley Arnold

DR. ARNOLD: Thank you. Lesley Arnold here. And, unfortunately, Rob could not be here today. Ironically, he has a pain condition that he's dealing with.

When we came to this meeting, we had a lot

Page 42

of barriers. Happily, we were able to overcome many of them, surprisingly in the fibromyalgia world. As many of you know, we have a history of some established criteria, dating back to 1990, and more recently some revisions to the criteria for fibromyalgia. I think we came to a consensus that we need to reevaluate how we approach the diagnosis of fibromyalgia, and this is a great forum for us to be able to do that work.

Our approach to Dimension 1, we followed the plan set forth by this organization. What we came to in our proposal was that Dimension 1 should include only symptoms, and this is what we came to consensus on. And this would include chronic, widespread pain, which we all agree is the core symptom of fibromyalgia.

However, with the way that the field has evolved from 1990 to the 2010-2011 criteria, something about the definition of chronic, widespread pain got lost. There was a difference in terms of how much of the body's affected versus how many points or, if you will, counting up the

Page 43

regions, et cetera.

So we felt that there was need now to go back to our existing databases to really evaluate the best way to define chronic, widespread pain. Is it localization three out of four quadrants or above and below the waist plus bedside, or a count of sites? And fortunately, we have some excellent researchers and people who have rich databases, and Gary is going to take the lead on this to help us evaluate this question.

We all agreed that this symptom of chronic, widespread pain being the core symptom of fibromyalgia is absolutely required. But we also recognize that patients have other associated symptoms that we thought are very important to consider.

Among the group, we all felt fatigue and unrefreshing sleep were the two most important symptoms, and these turned out to be very common in patient reports and in the other criteria and analyses that have been done. But we also recognize -- and I'll come back to this in a

Page 44

second -- that there were other symptoms that we needed to consider and perhaps include in a study.

So we wanted to come back in our reliability validation study and include a question about the following symptoms -- again, most days for the past three months, fatigue, unrefreshing sleep -- and also to rate the level of severity on a zero to 3 scale and also include these other symptoms.

We ultimately believe, but we don't know yet, that it will end up being just fatigue and unrefreshing sleep that will end up being part of the core criteria in Dimension 1, but we are going to leave that for the research to help us decide that.

Now, other issues that we addressed in Dimension 1 were the differential diagnosis considerations, which I'll come to in the next slide. We also have our plans going forward for studies, again reviewing existing data sets to assess the chronic, widespread pain definition and other core symptoms.

We also wanted Gary to evaluate in his

Page 45

assessment of chronic, widespread pain whether there was indeed sexual dimorphism in the comorbid symptoms like fatigue and unrefreshing sleep because that will inform our reliability and validity study because the other groups are grappling with how to do that study.

We had thought that using the 1990 criteria to categorize patients with chronic pain as fibromyalgia or non-fibromyalgia would be a good first step. However, we recognize that the 1990 criteria do bias the diagnosis towards women who are naturally more sensitive to the tender point exam.

So we're hoping to learn more about sexual dimorphism when we evaluate, again, those data sets that look at chronic, widespread pain and the relationship of that with some of the existing symptoms. So that will hopefully inform our study going forward.

As far as differential, I put this up. And it was really hard to read. Everyone was getting a big headache. But it just gives you an idea of the

Page 46

sense of what we consider in our usual evaluation of patients. And of course this would be included in our differential diagnosis, and there are others that aren't on here that the group is going to accumulate. But it gives you an idea of -- some sense of what the disorder is, what are the differentiating signs and symptoms, and any other tests that are used to evaluate these other conditions. And it gives you a flavor for what we're thinking going forward.

Moving on to Dimension 2, we wanted to include other common features, firstly, the common pain characteristics. And a history of a lifetime multiple other pain conditions was a very important part of the characteristics of these patients to help us identify them.

The pain tends to worsen with common mechanical stimulations, such as blood pressure cuff being hugged, tight clothing, et cetera., the pain being difficult to localize precisely; moving from place to place; a variable onset often difficult to describe; commonly, though, a deep

Page 47

tissue ache but can have neuropathic pain characteristics such as burning. Exertional pain is a common feature or also worse with inactivity or with stress, and the severity waxes and wanes.

So this is a flavor for some of the common pain characteristics that we felt in our group were important to note in Dimension 2. There may be others. This is a beginning of our work in defining that.

Dimension 2, we did include our signs. And here's where we thought tenderness could go. We wanted to move it out of Dimension 1 but include it in Dimension 2 as a potential importance to some clinicians and researchers who wanted to assess tenderness. And it can be done by doing the 1990 exam.

We have something called the Clauw exam that we're going to include. He had put his tenderness examination in a recent JAMA article, so we put that as another option, which is an abbreviated version of an exam. Skin-fold tenderness is in deference to Rob, who likes to use that in his

Page 48

exam. So there are other possible approaches to assessing tenderness. Another sign that some thought were common enough to include in Dimension 2 were signs of dysautonomia.

Then there were non-pain features. And again, this would include any of those non-pain features that end up not being part of Dimension 1 we would put down here in Dimension 2. Other things include depressed mood and anxious mood. And notice that we use the term "mood" here. So we're not talking about the major depressive disorder, which we will include in Dimension 3 as a comorbidity. So now we're just talking about symptoms of a mood, disturbance. Balance problems, again, something from Rob's work that we included.

This dimension, we also began to discuss epidemiology and discuss the importance of family history, age. And again, here we talk about juvenile onset and other more common ages of onset in adulthood. The sexual dimorphism question is very important, demographics, prevalence.

We have a fair amount of data now on

Page 49

worldwide prevalence of fibromyalgia that will be included. There's some less evidence of incidence, but there are some data, and a considerable amount on new onset. And then we wanted to address course, including prognosis and changes with aging. And some of these may be federal issues, but we wanted to put down what we thought was unique to fibromyalgia.

We touched on the comorbidity issue. This is just a subset of what we talked about. Other things that we would include in addition to these pain disorders, that seemed to overlap a great deal with fibromyalgia as well as a psychiatric disorder, are things like sleep disorders, Ellers-Danlos syndrome, myofascial pain syndrome, restless legs, other autoimmune disorders, inflammatory arthritides, degenerative musculoskeletal diseases, arthritis, obesity, chronic, viral illnesses, et cetera.

So we're working together as a group to pool together the common comorbidities in these patients.

Page 50

So here we are to myofascial pain. We had one sole representative in our group. He was helpful in getting this started. Dimension 1 would include both symptoms and signs, and both will be required. So symptoms would be acute or chronic regional musculoskeletal pain, and the signs would be the taut band in the muscle and tender spots in these taut bands that are reproducible. They reproduce the musculoskeletal pain upon touch or palpation.

Then as far as Dimension 2, there were other characteristics, trigger points, which include aspects of referred pain, a local twitch response, a needling, an autonomic response to palpation or stimulation, the fact that myofascial pain is often precipitated by injury or repetitive or sustained muscle loading. It can be associated with visceral pain such as pelvic pain and can occur in one or more regions. Not typically characterized as diffuse, but there are cases of widespread myofascial pain, so we wanted to acknowledge that.

Also, weakness is a characteristic and also

Page 51

restricted range of motion. But we recognize that we probably do need additional input. And here's a list of people that we think could be invited to join us. And we believe now -- and we probably want to check with our group overall whether we do want to create a subgroup and a separate manuscript for myofascial pain syndrome, being that is has its unique characteristics.

DR. BRUEHL: Questions?

DR. ZELTZER: So when you talk about age, is that through the data or is that through retrospective getting past histories on adults with fibromyalgia? So the question is, when does fibromyalgia really start, and does juvenile fibromyalgia in children and adolescents progress to adult fibromyalgia or is it a very different condition?

DR. CROFFORD: Our group feels that the signs and symptoms are essentially the same in juvenile fibromyalgia versus adult onset fibromyalgia. We took the charge from the committee that in Dimension 2 we should describe

Page 52

the epidemiology. And so what we listed up there was the work that we intended to do to put in the epidemiology section of Dimension 2.

DR. ZEMPSKY: I guess to follow up on Lonnie's question -- Bill Zempsky -- are you going to use existing data sets from the pediatric fibromyalgia leaders? Because I think that's going to be important.

DR. ARNOLD: Yes. This is Lesley Arnold. I work closely with the group at the Cincinnati Children's Hospital, where we have been doing a longitudinal study of juvenile fibromyalgia. So, yes, absolutely we're going to draw on that information.

DR. CROFFORD: Well, to be clear, for the first study, where we're trying to look at what's the best way to describe chronic, widespread pain, that study that will be in Gary MacFarlane's group is adults. But once we get to the validation of the criteria, we'll do additional studies looking at adults and children.

DR. FARRAR: John Farrar. Two questions.

Page 53

One I think is quick, which is what's the gold standard. And I assume it's expert opinion. The second is, although these are clearly very different syndromes, they're often mixed up. And I think it would be a major service to putting them either in the same paper or next to each other so that the criteria that differentiate the two are clearly expressed. And I wondered what you thought.

DR. CROFFORD: So we agree, and we had a lot of discussion in our group about what are the distinguishing features. After sitting through this session and listening to Jan and listening to everybody else in the group, I think it might be useful to separate them into two papers back to back. And the issue, we'll leave that to the organizers. I think we could do that either way.

DR. FARRAR: And differentiate between the two.

DR. CROFFORD: And differentiate between the two. I mean, the truth of the matter is we had lots of discussion about what was the same and what

Page 54

was different. And I think we've philosophically come to the agreement that when we think of myofascial pain, we think of a peripheral pain syndrome.

When we think of fibromyalgia, we think that there's necessarily a central component to it. And we tried to put in the myofascial pain that it was not widespread, kind of clearly identifying that regional or peripheral focus on how we think about myofascial pain. But again, we only had one person, and I think it's going to be very important to have a bigger group think about myofascial pain and help us.

DR. FARRAR: The group here is the converted, and so I think you've got us convinced or at least we've been convinced over time. But I think that the majority of the world still thinks of these as being nearly the same, and I agree they're not. But my point is, a table which indicates what's what, what the symptoms are that differentiate, in either article or maybe both, would really help.

Page 55

DR. CROFFORD: Thank you.

DR. BRUEHL: We've got time for a short question.

DR. S. DWORKIN: With regard to taut bands and trigger points, in our TMD group, we could not define them. And we found the inter-rater reliability so poor that we eliminated them from contention. And that was a long time ago, and hopefully things have changed. And the way around it would be simply to provide very careful operational definitions of taut bands and trigger points to justify their inclusion. And the research would determine whether your definitions were reliable or not.

DR. CROFFORD: Jan, did you make note of that?

DR. DOMMERHOLT: This is Jan Dommerholt. As the one representative of the myofascial pain person, I felt very lonely in the group of fibromyalgia people, I must say.

(Laughter.)

DR. DOMMERHOLT: When the TMD criteria were

Page 56

done, there were very few, if any, reliable studies on the reliability of trigger points and things. That has changed dramatically since 1997. There are several intra- and several good inter-rater reliability now in the literature and more to come, actually. So I think that problem is a problem of the past. But I agree that it should be defined what it is.

DR. BRUEHL: Our next group, we have Temporomandibular Disorders and Other Facial Pain. The chair of the working group is Werner Ceusters.

Presentation - Werner Ceusters

DR. CEUSTERS: The take on here is a little bit different. Instead of summarizing in 10 minutes the last day, I was asked to summarize my three-year collaboration with TMD groups, specifically with respect to ontology, which is kind of a new word I think for most people here in the room.

It grew out of my participation in the Miami international consensus workshop on convergence on orofacial pain taxonomy, where one of the

Page 57

conclusions was that we should put more emphasis on the terminology and ontology of pain as it is currently defined. And that resulted in a funded grant by NIH, through which I have been working with them.

Now, the reason for my invitation was the fact that it was observed that many classifications and taxonomies, developed by very intelligent people, have problems. This one for instance is MeSH. It's an old system, but it's updated regularly. This is from the last year still.

Wolfram syndrome is classified in something that seems to be a very reasonable structure if you know something about Wolfram syndrome. However, if you would use it as a diagnosis, and you say, "I have Wolfram syndrome," then it means also that I have an optic atrophy and that I have an optic nerve disease and so on. And that goes for all those things. But I tend, then, to have also a female urogenital disease. That's what MeSH claims.

We used our analysis to analyze the

Page 58

definition of pain provided by the AISP [sic], and there we discovered that actually in one definition, they are defining five different things. There's nothing specifically wrong there, but if you do not look carefully, you are not aware of that.

Another example is the international headache classification, ICHD, International Classification of Headache Disorders. So look at the painful, trigeminal neuropathy, which is stated to be a kind of trigeminal neuralgia. Look at the same time at the definitions. They have neuralgia, pain, and neuropathy, and now you see it doesn't make any sense. It should be the other way around.

So this here is a problem where no adequate tools have been used to see whether the definitions finally fit the taxonomy or the other way around. So I have been working now for 30 years in trying to prevent these kind of things in various domains. And it's only by coincidence that I became involved in these pain domains.

So the trick here is ontology, which is a

Page 59

kind of philosophical discipline, which is a part of metaphysics. Where metaphysics study how the world works, ontology studies what type of entities exist in the world. So you can have discussions among ontologists, where the pain exist, and some will say yes; others will say no. All ontologists, nevertheless, agree metaphysically that patients who suffer from pain -- and now we have to use quotes -- do exist.

So the task is for others -- so what do you take into your ontology and what do you not take into your ontology, and what do you need to describe in different ways. You can apply that in different ways. So this is for statisticians absolutely no problem. It says that what you measure is not really what you are thinking you are measuring because there are errors, systematic errors and random errors.

Ontology can help to tell you something. For instance, does that Vr, which is the real value, does it really exist? Identities are involved in bringing about that systematic error

Page 60

and that random error. And if the Vr really exists, how does it relate to those errors? You can figure those things out. If you have multiple things that you are testing -- in pain patients, you test multiple things -- ontology can help you already in telling how such things that you measure relate to each other without doing statistics.

There is a second sense of ontology, which came up in the mid '90s that is kind of a system, so kind of a super taxonomy. That's the way that I would classify it. The idea is if you have something nicely designed like this with formal relations between your things, for instance, you can use that to describe data unambiguously.

You can describe very clearly that that little one there in the spreadsheet about some TMD thing actually means that this patient with such and such patient identifier is stated to have a panoramic X-ray of the mouth, which is interpreted to show such and such and such; all that in a little one. In your databases, that is there implicitly. It is not explicitly in there.

Page 61

You can connect different kinds of data sets, and then you can see how they match up with that very unique ontology there. If you do that -- now, for instance, you can see that here if you do a statistical analysis, you see that characteristic 1 and characteristic 4 statistically correlate, I as an ontologist wouldn't say, "Duh, it was already there in your ontology." Right?

On the other hand, if you find by doing your statistical analysis that they do not correlate, then there is probably a problem in the ontology or in the taxonomy. So you can make this work in both ways. So there is a caveat.

So the computer science approach to ontology does not take the philosophical principles into account, and now you get some problems. Most of the approaches use what is called the semiotic or the semantic triangles, for when we use a certain word like "dog" -- that's displaced there -- you think you have the concept of a dog. And it actually refers to things that walk on the street, and that bark, and so on.

Page 62

Now, that's very heavily used in medicine as well. There was the term "drapetomania" in psychiatry in '84. Probably, you don't know what it meant, but it was a disease which caused the slaves to suffer from an unexplainable propensity to run away.

(Laughter.)

DR. CEUSTERS: I found that in the Buffalo Medical Journal of '84.

Of course, you need to apply principles to what you put in your taxonomy. Many do that already. Here is a list of ontologies which are free to use, which are curated, which are updated regularly, and which describe organisms, anatomical entities, organ functions, phenotypic qualities, biological processes, molecular functions. All that exists to use it.

If you do it that way, instead of just relating your ideas there, you can relate in different ways. So this was how beliefs are taught to be related. The bottom-right corner, you can use it to express how the actual reference, what

Page 63

you are describing, are related. It was actually true that slaves had a propensity to run away, but it's not true that it was a disorder. You can relate the terms to each other.

Now, this drapetomania, the term itself tells that it's a mania, so a disorder. And "drape" comes from the Greek, running away. So it makes some sense to have that kind of term. But at the same time, how sensitive are patient advocates not about what terms you give to diseases? So there are rules that should be applied to that as well. So that's that aspect.

There is the ontology of general medical science, which has described a couple of fundamental notions in the diagnostic process and how disorders and symptoms and everything works. Doesn't that look very close to the kind of dimensions that you want to have in your system?

The nice part here is that all those relationships are formally defined so that humans can understand it, machines can understand it and can reason with it automatically. One of the

Page 64

advantages here, for instance, is a clear distinction between disorder and disease that some already brought up and the one with diagnosis that I brought up, diagnosis in the head of the physician, and the rest is there.

It is, for instance, used in cirrhosis and other examples. People are using these to characterize diseases. So in this case, cirrhosis is due to environmental exposure, while the etiological process is a phenobarbital-induced hepatic cell event [indiscernible]. The disorder is a necrotic liver. The disposition, which is the disease, is the cirrhosis. The pathological processes involved are abnormal tissue repair with cell proliferation, and so forth, and so forth.

Now, the elements themselves -- so the values that you put in your axis there, they are taken from the ontologies that I have just referred to on that sheet. So what you need to do is to bring those things together in your specific domain.

There are some principles for the

Page 65

ontology-based taxonomies. One principle is be explicit with assertions about particulars or types of individual patients or groups of patients. I have had people -- I've heard people arguing about the existence of a mixed gender. And what they actually were talking about was populations of cows. And some populations were composed of 60 percent of male cows, 40 percent bulls, and the other rate.

So the way that they wanted to represent it is not to have just male gender and female gender, but also to have a mixed gender. The mistake there of course is that you are trying to define characteristics which is inherent to a single entity to a population. You shouldn't do that. I'm not going in to detail because I've run out already I think in my 10 minutes.

But these different principles all are violated in the international headache classification. Look at this persistent idiopathic facial pain, for instance. You can imagine that you have three different types of pain. For

Page 66

instance, my pain, her pain, and his pain. So there are three different instances we call it. My pain might be such that all the time it has presentation type 1, which is a combination of certain symptoms, which goes into your Dimension 2. Her pain might be of a different nature. So time 1, it is presentation type 1. Time 2 is presentation type 2 because a symptom disappears or another came in and so on. And you can have another configuration for his pain.

Now, why is that important? Well, if I read those terms, and I look at the definition in ICHD and they don't say whether that is about types or about instances, if it is about types, then those three particular pains -- those three different pains -- they fall under the same heading.

So when the description is about particulars, then only her pain, the middle one, falls under there. Why is that relevant? I mean, it's not just building a taxonomy that you do. You want specific patients to be classified under one of them, under those categories. Well, if the

Page 67

classification is built in such a way that you can't do it, you have a problem.

The second one, and that's the last one I'm going to show, what are you exactly going to classify? ICHD is not sure about it. Disorders is in the title, International Classification of Headache Disorders. But then is it headaches you read in the introduction? Many questions are not needed in order to classify primary headaches, et cetera, et cetera. Is it patients?

The second edition will hopefully further promote unity in the way we classify, diagnose, and treat headache patients throughout the world. Patients are not disorders and are not headaches and so on.

Conclusion. Realism-based ontology. That has a lot to offer to build faithful representation, but it's hard. You have to do a little bit more work than what you normally would do. But you can ask for help of skilled ontologists. Pain classifications, and for all other classifications made by domain experts, they

Page 68

would benefit. Now, domain experts are not ontologists and the opposite way around, so we need collaboration.

The problem might be there are old habits under this mainstream thinking, and there is guru-ism. But I honestly think that hampers the advice of science, and sometimes we need to rearrange things in the way that we are used to. Thank you.

DR. BRUEHL: We do have a couple of minutes left for questions. I would ask -- this hopefully is a 1-minute answer or question. I have not really been thinking about what we're doing is coming up with diagnostic criteria. Implied in that in my head was that we're trying to capture some underlying disorder disease. But the truth is, the way we plan on using it is to identify patients who have the disease.

Is what you presented there, would it have a practical -- how would that change, practically, what we do when we're coming up, for example, with Dimension 1 to list how to diagnose a given

Page 69

patient?
DR. CEUSTERS: Well, it will help you when determining -- I heard a couple of good questions a couple of times. It will help you in determining, for instance, what goes in Axis I and what goes in Dimension 2 and in Dimension 3. So there are certain principles that we can apply for that, and that is one thing.
DR. BRUEHL: Okay.
DR. SARZI-PUTTINI: Can I just make a comment? I think these ontologists are really very interesting. But the point is, when you talk about pain, you're talking about subjective symptoms. And we are also missing some of the pathophysiological mechanisms.
So in a way, we cannot follow what you are saying. We have to realize that we have to group these symptoms because, otherwise, each patient will be a different patient. So we would have to do a classification of pain that is individualized and is not instead put in together.
Ontology is okay when you have objective

Page 70

symptoms. When you have subjective symptoms, it doesn't feel as much for --
DR. CEUSTERS: It applies in exactly the same way because what is objective in that case is what the patient says. So when you work with what a patient says in contrast to what you see, you can correlate them.
What ontology is about is about figuring out what the entities are and how they relate to each other. Objective or subjective, I mean, it's for ontology all the same in the sense you can deal with them in the same way. I'm not saying that they are the same things, but you can deal with them using the same principles, and in that way not making mistakes or eliminating certain mistakes.
DR. BRUEHL: Thank you. Next, we have the Visceral, Pelvis and Urogenital Pain group, including IBS and IC. This is Nicholas Verne and Ursula Wesselmann.
Presentation - Ursula Wesselmann
DR. WESSELMANN: While Nick is putting up the slides, I just wanted to say what kind of group

Page 71

we were because we were a very diverse group with a lot of different expertises. For abdominal and pelvic pain, we had GI expertise, which is Nick Verne from Galveston; and Qiqi Zhou from Galveston, basic scientists; and Linda Li from Hopkins.
For gynecology, we had Mary Pat FitzGerald from Chicago from the VA; Gloria Bachmann from Rutgers; and Andrea Rapkin from UCLA. For urology, it was Quentin Clemens from Michigan; Chris Payne from Stanford; and Robert Moldwin from Long Island Jewish Medical Center.
Because a lot of these abdominal and pelvic pain syndromes start already in childhood, in adolescence, but there is less known about it, we had two experts in that area, Lynn Walker, from Vanderbilt, who is a psychologist; and Lonnie Zeltzer from UCLA, who is a pediatrician; and then myself, Ursula Wesselmann. I'm a neurologist with specialty training in pain management.
We started out trying to fit the different pelvic and abdominal pain syndromes into the grid that was provided to us or that is in the paper

Page 72

that is provided to everybody, that Roger was the first author, and we had some difficulty with it. We will show you an example using bladder pain later on, and we went through the exercise as well for gynecological pain and also for itchy eye pain.
But we came up with a more general term, which I want to present here for discussion because we discussed it a lot over the last two days. Abdominal and pelvic pain present as pain or discomfort -- so it's not necessarily always pain localized to anatomical regions in the abdominal and pelvic area -- for at least three months duration. And three months was suggested at our initial get-together yesterday, to use three months for most of the pain syndromes we want to make a taxonomy of.
But we also wonder if it can be longer or less, especially -- Lonnie had pointed out in the pediatric population, the diagnosis is often made after a shorter time, whereas we who see adult patients usually see the patients and make the diagnosis after they had the symptoms for a long

Page 73

time just because of the logistics, until they get an appointment.

Abdominal and pelvic pain is often considered just as visceral pain, but there is visceral somatic interaction. So we have actually visceral-visceral interactions from one visceral organ to the other, and we have visceral somatic interactions. And what is often not thought about it is there is also somatic visceral interactions.

So patients, for instance, who have burn injuries to the cutaneous and muscular structures also have visceral hypersensitivity. And in the animal literature, there are experiments where you inflame muscles in the lower back or in the upper legs, and you can demonstrate visceral hypersensitivity. So it can go both ways, and we are often not so aware of it.

So we put this on top, somatic and visceral mechanisms and somatic and visceral presentations for these abdominal and pelvic pain syndromes. And below that, you see a category with organ-specific symptoms and without organ-specific symptoms.

Page 74

With organ-specific symptoms -- I will give you an example later -- bladder pain or irritable bowel syndrome. We went through that exercise but did not present it here. Vulvodynia is another example, where there are very specific symptoms, as we see it also with other pain syndromes. For example, with headache, you have migraine headache, cluster headache, which has very specific symptoms, and then others are just pain in the head, basically.

So both of these presentations, with or without organ-specific symptoms, will need a diagnostic workup, but the specifics of the diagnostic workup might be different. So these patients typically have a gynecological, gastroenterological, urological, urogenital, somatic -- somatoform -- workup. But it will be different because, obviously, if there are no organ-specific symptoms, you will not do some of the procedures that are targeted to a certain organ.

So all these mechanisms and etiologies,

Page 75

however, have to be considered. And with somatic, we meant that many of these patients have myofascial pain features. They might have a neuropathy where you would actually inject an entrapped nerve, and the pain syndrome would go away, and you might have cutaneous hypersensitivity. And with somatoform, we tried to indicate that some psychiatric disorders can present in the differential diagnosis with abdominal and pelvic pain.

With organ-specific symptoms, we have examples, really, in every category, for GI, for pelvic, gynecological, for urologic, and also for the pelvic floor for the external genitalia. As an example, here in this diagram, we have presented a GI where the Rome criteria -- a very well established criteria for IBS. And there's a certain differential diagnosis that is included in those criteria.

I don't want to go through the other examples. I will just show you our example on bladder pain. You probably have heard interstitial

Page 76

cystitis, painful bladder syndrome, and bladder pain syndrome. So there are many different words actually for it.

This is a table out of a review paper that came out in Pain two years ago that Chris Payne, who is in our working group, had published. And it just shows -- briefly, for those of you who are not so familiar with bladder pain -- how the taxonomy moved from focusing on organ pathology in the bladder -- those were Hunner's ulcers or glomerulations -- to a chronic pain syndrome in the bladder.

In the current definitions, bladder pain is defined as an unpleasant sensation, pain, pressure discomfort perceived to be related to the urinary bladder, associated with lower urinary tract symptoms, urinary urgency and frequency and other misconceptions of the -- or misfeelings, really, of the bladder in the absence of infection or other identifiable causes. This definition is also endorsed by the American Urological Association in the IC guidelines that were published in 2011 and

Page 77

are currently being revised.

So it started out, actually historically, a long, long time ago before the NIDDK criteria for research were established about 20 years ago. It started out with thinking that this was some pathology that is in the bladder, and now it has moved to understanding bladder pain as a chronic pain syndrome.

So we tried -- rather than trying to find a new name for it, we called it bladder pain for our exercise here. For Dimension 1, for the core diagnostic criteria, we decided to stick with the American Urological Association criteria, which require pain, pressure, and/or discomfort in the bladder area for a period of at least three months, excluding other diseases that could mimic bladder pain: cancer, stones, hematuria, and neurogenic bladder.

Importantly, in order to exclude those diseases, a cystoscopy might be required and further invasive urological workup, but it is not required for the diagnosis of bladder pain.

Page 78

What are the common features? So we moved on to Dimension 2, and we could extend this list -- there is actually a lot of literature spread out in many different journals about this. So there's nocturia, dysuria, pain with ejaculation in men, hesitance, decreased flow. I don't want to read this all to you. It's just an example, also, of the research that we could go into as a group to verify some of this information.

Epidemiological aspects. Bladder pain and many of the pelvic pains are difficult to study because they are waxing and waning symptoms. Bladder pain usually presents in young and middle-aged females, and the female-to-male ratio is 5 to 1. So if you find bladder pain in an elderly patient with new onset, that is usually a red flag.

Comorbidities, we have a whole list, and it can be replaced in many cases by the lists that were previously shown from the other working groups. We grouped many of the pain syndromes together as functional somatic symptoms, the

Page 79

psychological/psychiatric comorbidities as negative affect, ultra-immune diagnosis, endometriosis. So a pathology, actually, in the pelvic cavity is often associated with bladder pain. Functional bowel disorders. Autonomic dysfunction is something that is currently being researched for bladder pain and the history of abuse and trauma.

Dimension 4, again, we find many of those consequences that are really quite typical for all the pain syndromes that are studied here. What is important for the pelvic and abdominal pain is sexual dysfunction that is more prominent than for many of the other pain syndromes.

Again, the mechanisms are similar to what has been presented. Before, the focus is currently on pain mechanisms, central and peripheral. The reproductive history aspects play a role. Autoimmune mechanisms have been demonstrated. Search for bladder abnormalities have not been so successful so far, and an important aspect of research is actually to start in childhood. A lot of the studies on bladder pain have only included

Page 80

patients as of the age of 18 or 19, depending in which state you live.

Can I have the last slide? I briefly wanted to say we were a multidisciplinary group with physicians and researchers from different specialties who all see abdominal and pelvic pain. And we actually rarely get together, so this was a great forum for us to discuss and exchange ideas.

It really requires a setting also in the healthcare system, where we can work together for this particular patient group because right now, the taxonomies, were made and are focused on the different abdominal pelvic organs. But as we showed in the first slide, it is probably more useful, for studying the etiology and for treating those patients, to start out from a global level of abdominal/pelvic pain, and then move down.

In Britain, they are already at this stage. The government a few years ago implemented that there should be pain pathways for these patients, not only the pelvic pain patients but also other pain groups. And this concept needs to be

Page 81

implemented also in the medical school training for the medical students and residents. So I just wanted you to be aware of this government effort in the UK. Thank you.

DR. BRUEHL: Thanks. We don't have much time for questions. Is there a burning question?

(No response.)

DR. BRUEHL: No? Okay. Let's do Cancer pain with Judy Paice.

Presentation - Judith Paice

DR. PAICE: While we're pulling up those slides, I'm Judy Paice from Chicago. We had a robust committee with an interdisciplinary, international perspective. We'll see that list in just a moment.

My co-chair is Tom Smith, who is a physician at Hopkins, does palliative care, and he was unable to be with us today. Michael Bennett and Matt Mulvey from the UK also couldn't be with us. They began the hard work of this committee by conducting a systematic review of the literature related to cancer pain syndromes, and that review informed our

Page 82

work for these past two days, and it continues.

We have the advantage and disadvantage of not having any preexisting classification systems, really, for cancer pain. We developed four conditions or we identified four conditions, both through the systematic review and from the advice of the committee.

So we started with bone pain, and we particularly specified without radiculopathy so there wouldn't be overlap with the low back pain group. And we were trying to ensure throughout this entire process that we were being so specific that we could clearly discern is this a cancer-related syndrome and how is it different than some of the other syndromes that have been defined in the past two days. So we tried very hard to adapt to this system, the different dimensions. We have the symptoms, pain in one or more locations, it increases over time.

I should take a step back. There were several ways in which we identified cancer pain being very different -- any of these conditions

Page 83

that I'm going to be describing -- very, very different than some of the others that have been defined already. One is in the timing. There's no way that we could state that three months needs to be that magic time period before we would call it a chronic pain syndrome. So that's one.

The second is that this is a dynamic phenomenon with cancer pain and that as we're looking at the actual syndrome or condition, there are also changes going on in the tumor. The tumor is maybe getting bigger or hopefully responding to our treatment. And then the other variable is that the treatments are being administered, and there's usually more than one treatment, which makes it somewhat complex to specifically define a time course or an epidemiology.

We had a really fascinating conversation before finishing today, where Pat Dougherty mentioned that we should probably come up with a morphine-equivalent daily dose for some of the neurotoxicities of some of the agents. So most of our patients don't get one neurotoxic drug; they're

Page 84

getting multiple agents. And so is there a way that we could come up with an equianalgesic ratio, if you will, that would be reflective of the neurotoxicity ratio so that some of our patients may get X amount of paclitaxel. They might get X amount of another neurotoxic agent. How could those be defined and combined to give us some sort of indicator of the risk for patients with chemo-induced neuropathy?

Then throughout all of these is the contribution of the tumor microenvironment. And Brian Schmidt was wonderful in reminding us throughout about the underlying genetic profile of the cancer, but also the microenvironment produced by this tumor and how it's also contributing to these pain syndromes.

So back to bone pain, we have pain in more than one location. Clearly, the individuals have a cancer diagnosis and then generally defined through the diagnostic testing imaging. The pain is worse with movement, with pressure. In other words, the patient stands, and they have severe pain. And

Page 85

these patients oftentimes have no pain when they're lying flat but severe pain when standing, or if the pain at the bone metastasis is in the upper extremity, for example, it's pain when lifting something or picking up something.

You can see there's no minimal duration, and then the functional consequences that might be different -- we kept trying to ascertain the difference between cancer and other syndromes -- is that with the decreased ADLs, these patients are at greater risk for the complications of cancer such as deep vein thrombosis and others.

I'll move on. The second we defined, and we began by calling this CIPN. It's what most of the literature refers to as chemotherapy-induced peripheral neuropathy, although we are now beginning to use biologics, which are not technically chemotherapy type drugs. So overall, these are drug-induced peripheral neuropathies in cancer, and yet since the nomenclature that most know is CIPN, we're going to call it that.

It's pain, at least as described by

Page 86

patients. But not all will use the word "pain." Many will use the word "discomfort" but it's always in the face of something unpleasant. And I sort of heard a little of that today as other groups were describing their conditions; generally described as tingling, numb, and burning. Again, the factors that need to be in place are cancer diagnosis and that it's definitely treatment related.

So we clearly have a drug being administered, and then in a time course that's somewhat anticipated, the individual will then report these sensations. And we can see some of the other signs like the balance and proprioception changes, which we think might be somewhat unique to chemo-induced neuropathy.

In fact, when Rob Edwards and I were kibitzing afterwards, trying to make sure we were all on the same page, that would be an interesting research study and a relatively simple one for a fellow or a grad student to compare the experiences of the person with diabetic neuropathy with the person with chemotherapy-induced neuropathy.

Page 87

Here are the other dimensions, the temporal onset consistent with the administration of the chemotherapeutic agent. And again, emphasizing that proprioception change occurs, leading to falls and other really serious consequences on the quality of life for those patients. The neurobiologic mechanisms we're beginning to understand through work that Pat is conducting, Pat Mantyh is conducting, and others.

Our third condition that we selected was pancreatic cancer. And we chose this as an exemplar of pain related to the tumor. And the reason that we chose this is that it has global implications. It has lousy survival rates regardless of whether you're in a developed country or the developing country.

So we wanted to reflect not just our advanced medicine views where we have sophisticated diagnostic techniques and sophisticated therapies, but we wanted to reflect a syndrome that would be a problem regardless of where you might live throughout the world.

Page 88

So it's pain at the site, in the right-upper quadrant in general. It may refer to the back. It increases with time as tumor progression advances. It may radiate. We don't know that for sure. We have a lot of questions, as you can see in these tables. It can be perceived as pain in the back as well, but it's very different than the back pain kinds of descriptors that you would see with someone who has tumor-related vertebral body metastases.

The common features are somewhat unique, with cachexia obstruction, and then depression. Yes, with all the syndromes we've discussed, depression is a comorbid condition, and yet depression seems to be a consequence. It occurs in a very different way than what we see with individuals who have chronic pain states. It can occur acutely, and it's profound. Hiccups, fatigue, and other syndromes can occur. And we believe that we need to begin doing genotyping to profile the microenvironment again.

The last one we tried to tackle is the

Page 89

post-cancer or post-surgical cancer pain syndromes. And we were looking at post-thoracotomy or post-mastectomy syndrome as a model. And again, this is where it's challenging. Is it post-mastectomy, post-lumpectomy, post-axillary node dissection, post-sentinel node dissection? So there were all these different variations that are being done to our patients.

So the signs, again, cancer diagnosis, the surgery, allodynia guarding, hyperalgesia, hypoesthesia, and there's the plus/minuses because we don't know. We need to better characterize these conditions.

The symptoms, this is where we acquiesce to the pain greater than three months, pain at the site, paresthesia, sensations of swelling, changes in activities of daily living because of the pain. Many patients report that they cannot sleep on the affected side, and that's true in Brian's head and neck cancer patients and Chris' breast cancer patients.

We were recommending, in terms of diagnostic

Page 90

techniques, quantitative sensory testing, again, for the research setting. We're not ready to go prime time for the clinical setting in making that a strong recommendation. We were fascinated by some of the common features that might put patients at risk, like perioperative events. I've learned that the word is not "complications" but "events" from a legal perspective, whether the individual gets infection.

The individuals who are more likely to have drains or chest tubes after a procedure, are they more likely to have more of a persistent pain syndrome if they had preoperative pain, poor postoperative pain control?

Neoadjuvant chemotherapy/radiation. This is in the setting for those of you who are not familiar with cancer, where individuals get chemo and/or radiotherapy prior to their surgical procedure to shrink the tumor to limit the invasiveness of the surgical technique. Are they more likely to have persistent pain when compared to people who never saw chemo or radiotherapy

Page 91

before surgery?

One of the consequences we identified was lymphedema, and, again, that's true across different tumor types. And then risk factors -- and I saw this in several of your explanations today -- the lower socioeconomic status, in part because patients have fewer resources. But probably a huge indicator for the cancer population is that these individuals are diagnosed much later because of their illness.

So that's where our group came up. We were under the wonderful leadership of Dr. Turk. Any questions?

Am I getting us back on time, Steve?

DR. BRUEHL: Oh, you're great. You've actually got 3 minutes and 15 seconds.

DR. PAICE: Thoughts, questions, concerns? No? Ursula?

DR. WESSELMANN: [Inaudible - microphone off.]

DR. PAICE: So the question is how do we assess the pain burden of the many different

Page 92

good --

DR. WESSELMANN: [Inaudible - microphone off.]

DR. PAICE: Good question. So patients rarely have one syndrome or one condition alone. How do we assess multiple conditions, the burden associated with multiple conditions? I don't think we got that far.

Group? Chris?

DR. WESSELMANN: Especially the temporal something, it might get worse, but something else might get better.

DR. PAICE: Right.

DR. WESSELMANN: [Inaudible - microphone off.]

DR. PAICE: That's what we were speaking to the dynamics of this. But, Chris, go ahead.

DR. MIASKOWSKI: Chris Miaskowski. Ursula, I love your question. I think it's a really critical one. And what we did talk about was the fact that the data is now showing that 50 percent of people who have a cancer pain problem also have

Page 93

a non-cancer related pain problem, so that whole interplay as well. And I think with the demographics of the society changing and the number of people who are aging who are predicted to have a cancer diagnosis in the next 20 years, it's going to become a much more complex problem to sort out.

DR. PAICE: We came up with a huge list of research questions and some wonderful opportunities with preexisting data sets that Chris has, Pat Dougherty has, and others.

DR. KHALSA: I just wanted to follow up on that, this idea of how do you measure the -- this comes back to the impact of the pain. And I just wanted to advocate for something that the NIH task force on low back pain -- which I think was very clever and I think is generalizable because of what they did.

So the task force was trying to assess the difference between pain intensity, which you can measure on a standard numerical rating scale or VAS, whatever, versus how this really impacts people, which takes into account really looking at

Page 94

pain function and pain behavior.

Because the task force in its minimal data set adopted a lot of the domains that the NIH PROMIS tool utilizes, a few of the members of the task force kept looking at that and said, "Well, gee. I wonder if we could sort of go beyond what PROMIS itself developed and try to develop an IMPACT metric using these PROMIS domains."

So the task force essentially came up and proposed and had some preliminary data to support the use of an IMPACT measure, which comes directly from the PROMIS measures. And it's a very simple, linear addition when you sum up some of these scores, and showed that at least for low back pain, it has equal validity, if not better, than some of the other functional measures that are commonly used in the back pain world.

So it's something that other groups might want to consider if they're looking at these domains that PROMIS addresses that gives you a very straightforward way of measuring impact of the pain itself.

Page 95

DR. MIASKOWSKI: Chris Miaskowski. I think this whole notion of functional appraisal is really, really important. In all the work we've done in cancer pain and symptoms, it's amazed me that this very simple scale that Karnofsky developed back in '49 -- okay, he studied nitrogen mustard, basically. And he made this scale that's used in oncology, that goes from zero, which is dead, to 100, which is fully functional in 10-unit increments. And the patient reports the kind of level of function they have.

It is highly correlative with every symptom we've studied. It's sensitive to different pain groups, mild, moderate and severe. And even in our breast cancer work, where we've had highly functional women in terms of our mild, moderate and severe pain groups, small changes in function were discriminated among those groups. So I agree with you that we need to fine-tune this metric in our pain taxonomy.

DR. BRUEHL: Thank you. And we're ready for our last group, the Sickle Cell Pain group, Carlton

Page 96

Dampier and Tonya Palermo. Go for it.

Presentation - Carlton Dampier

DR. DAMPIER: Thank you. I'd like to certainly thank the organizers for including this particular disease pain. We felt that we've come somewhat late to the party, so we're very grateful for being included and think that much of this work can very uniquely inform our community and assist our patients.

Our working group was myself and Tonya Palermo, and then a number of hematologists who treat both or either adult or pediatric patients, and then another pediatric psychologist, and Bill Zempsky, a pediatric pain person. So while we were not particularly international at this point, we were certain multidisciplinary.

This is one of the diaries that one of my patients completed over a several-year period, as you can see, quite a while ago. And this has been the understanding of what sickle cell pain is like, and really up until the 1970s and 1980s, in part, because many of the more severely affected

Page 97

individuals did not survive and live beyond childhood.

Now we're recognizing that many of the individuals, both in the adolescent age group and certainly in the adult age group, look much more like this. So again, someone, with except for some missed diaries, really seems to have persistent daily pain. And this is the group that we really felt it was quite important clinically to bring to the attention of both our clinical providers as well as to the pain community because we really have very little information about these individuals.

Certainly, they're unique features. It's certainly almost exclusively a disorder of minority individuals, onset and early infancy. And while frequent acute pain occurs in childhood, the persistent pain that we're seeing is relatively rare prior to the early teenage years, but then becomes remarkably common in adults. So there is we think much to learn and much to do.

Issues that we really had to struggle with

Page 98

in terms of this taxonomy exercise is it's really very limited, both research and clinical data, describing these pain conditions, and really very limited reliability of any diagnostic testing with a possible exception of certain complications that we'll describe, and virtually no data on etiologies or mechanisms.

We've proposed four different conditions, perhaps largest group -- although, again, part of the research agenda would be really to ascertain some prevalence of these various conditions -- is a persistent pain without any other specific painful complication of the disorder, and then a group of three additional conditions where there are well-demonstrated pathologies related to sickle cell disease, but not directly related to vaso-occlusion, that have separate diagnostic criteria and separate treatments and separate natural histories.

We struggled much like I think the cancer group did in terms of recognizing that the temporality of the pain is a very important issue,

Page 99

that this is really an episodic pain disorder. And we need to exclude those individuals who continue to have episodic pain and not persistent pain, and chose at least for our initial criteria a pattern similar to what the headache folks have done, which is a pain frequency on more than half of the days in a month.

Again, we're happy, at least initially, with a three-month period, although that's an area that, again, we'd like to be informed, as I'll mention later, by research and reanalysis of existing data sets.

The overlap between this persistent pain syndrome and the co-occurrence of acute pain is something that is, again, relatively unique to this disorder and whether that would need to be factored into a diagnostic criteria or whether that would simply be a common feature was, again, part of the information that we interested in obtaining, and again, whether the number and locations of the pain might be a diagnostic criteria or perhaps a common feature. Again, much like the cancer pain

Page 100

literature, there may be characteristics and descriptors that are important. But we really don't have sufficient data.

We then recognized that we have this, again, group of other conditions generally with bone or skin or visceral involvement, and in those we can use the diagnostic criteria that are available in the clinical literature as additional diagnostic criteria.

So where the group is now is really kind of working through what needs to be in common features versus common comorbidities and functional or psychosocial consequences. And there is some information that we can work from with the literature, although they're not often necessarily specific to chronic pain scenarios. So again, maybe an area where we need to develop a larger research agenda.

I tried to focus our current research agenda, for the purposes of this exercise, really around symptom prevalence and temporal patterns. We're particularly interested in the prevalence of

Page 101

these four conditions and recognizing that there may very well be co-occurrence of several of these conditions. And again, as a lifelong disorder, better understanding the [inaudible - intermittent mike] as they reflect either prevalence or perhaps diagnostic criteria.

From a funding perspective, we do have a few existing data sets that would be worthy of reanalysis for some of these considerations. And much of the time today was spent on developing a draft data collection instrument that we could use to address these specific considerations, with a caveat that we weren't sure how much additional data might be more global across these pain disorders and might need to be included in our data collection.

So that's where we stand and, again, would be happy to answer questions.

Presentation – Tonya Palermo

DR. PALERMO: Just to add, one of the discussion points for us -- and this is probably true for the cancer group, too, is what's an

Page 102

appropriate comparator. And our discussion was really around we can't really compare to someone who doesn't have the disease [inaudible - intermittent mike] -- we thought about was just collecting this data on all sickle cell patients and discriminating between those with and without a [inaudible - intermittent mike] persistent pain.

I don't know how the cancer group is handling that, but that was something we talked about as well.

DR. DAMPIER: Yes?

DR. FARRAR: I'm going to sound like a broken record. This is John Farrar. Do you have a sense that you're going to be able to collect data that might be useful in differentiating different types of pain syndromes in this population? Is that even a rational thing to think about? Are there patients with persistent pain that affects certain organ systems or for certain joints or other things?

DR. DAMPIER: Part of that is limited by our current understanding. But the expectation

Page 103

was -- and particularly over a broad age group and potentially across -- there are a number of clinical sites that we could have information on, on a broad range of these, for conditions, recognizing that some may commonly co-occur. Particularly in the adult population, it might be a little bit more difficult for us to have unique features of one particular condition, but that might very well be possible in the pediatric population.

DR. FARRAR: Just to follow up, I guess the question is how often do you see people who have one or the other as opposed to multiple combinations? And are there subgroups of this population that are worth looking at to try and understand something more about it?

DR. DAMPIER: Agreed, and certainly anecdotally, the experience is that -- for example, individuals with leg ulcers often may have that as an isolated symptom. Certainly in pediatrics, we may very well have some individuals who specifically have avascular necrosis without some

Page 104

sort of generalized pain syndrome.

So again, given a broad enough net, I think we can, to a degree. Now, there may be some age and other confounds that might make it a little bit difficult to broadly characterize across all age groups, all diagnoses, but we can make a stab.

DR. PALERMO: Even that first category, there has not been a well-defined -- or there's not a well-accepted definition of persistent pain in sickle cell disease -- category, in addition to current classification.

DR. S. DWORKIN: Sam Dworkin. I was wondering what accounts for the increased longevity that you now observe, and are there any hypotheses about how the increased longevity interacts with pain since the pain pattern seems to be observed --

DR. DAMPIER: No. It's an interesting question and something that we're beginning to struggle with as we look at fairly older data sets, data sets from the '70s, and compare them to current data. Clearly, the difference is related

Page 105

to our greatly improved ability to manage infectious diseases in these patients. So that has really been the profound difference.

Whether we're now indeed seeing a much more chronically ill population, I think that some of us with white hair certainly think that way. Whether we'd be able to really demonstrate that is going to be hard to say.

DR. S. DWORKIN: Chronically ill with regard to sickle cell with and without pain or the pain persists even though your interventions allow greater longevity?

DR. DAMPIER: Repeat that question again. I'm sorry.

DR. S. DWORKIN: The thing that's intriguing to me is that the longevity that you've depicted from the disease not progressing -- the individuals, patients not progressing beyond childhood into adult life doesn't seem to -- the pain patterns in the younger and older patients don't seem to be different. And so I was wondering what it was that was accounting for the longevity

Page 106

and its non-interaction with prevalence of pain.

DR. DAMPIER: We don't really understand etiologies and mechanisms, so I think that's hard to speculate on. Since many of these individuals probably -- we don't have data from the '70s and '80s because these individuals just didn't live long enough. It's interesting to speculate, but it will be kind of hard to prove.

DR. BRUEHL: Thank you.

MS. DARBARI: Can I add an answer to one of those things?

DR. BRUEHL: Briefly.

MS. DARBARI: Our collaborative study had shown that if you had more pain crisis, the life span was shorter. So I looked at the NIH database, which is like more recent because now we are using hydroxyurea transfusion and patients are living longer. So in this era, is pain still related to the shorter life span? So it was still positive and that we published.

So there is something. Either these are the patients who have more severe disease and die early

Page 107

or some other factor. So we also looked at some of the other factors that are high risk for early death, and pain was still very significant in that.

DR. BRUEHL: All right. Very good. Thank you.

We are running out of time, so let's do this. Let's take a 10-minute break for coffee, bathroom, whatever. It's now 3:09. So around 3:20, if we can come back, we want to kind of have an overall wrap-up of things and get everybody out of here by 4:00.

(Whereupon, a recess was taken.)

Next Steps

DR. FILLINGIM: Okay. Let's go ahead and get started here. So we've got a wrap-up session here. I'd like to say, if you'll look at your agenda, my name is not on the list during this segment, and I was ambushed shortly before the break.

(Laughter.)

UNIDENTIFIED SPEAKER: It was a typo.

DR. R. DWORKIN: It's a demonstration of

Page 108

Fillingimectomy [ph].

DR. FILLINGIM: Yes. And before we get started, somebody asked me about disclosures at the break. I'll say two things about that.

One is, we sent a form to everybody because we want to be able to say, if we're ever asked, that all potential conflicts and relationships of AAPT participants and principals were disclosed to us. So if you haven't sent that form back to Cassie Corvo at the American Pain Society, please do. And if you're not sure whether you sent it back or not, email me or email Cassie, and I think we can tell you.

The other question that came up is when you're doing other disclosures, do you now need to disclose this relationship? And I think that depends on your institutional guidelines and what they think a disclosure is. I don't think we have stock options in ACTTION now. So for many definitions of disclosure, it would be no, but you'll have to look at the fine print and your institutional guidelines.

Page 109

Does that help? Okay.
So we've had a great couple of days as far as I can tell. We've heard from each of the working groups, excellent progress across the board. I'll just mention one or two cross-cutting issues that I know came up in the group I sat in on and I've heard from other people, and then we'll open the floor for discussion and questions and so on and so forth. And many of these questions revolve around the research that will be done and what that's going to look like. And I just spoke with Bob.
So one proposal that came out of their working group was AAPT 1, which is what we're working on now, will be published -- each working group will publish their AAPT 1 classifications using literature review and existing data that they currently have access to and can reanalyze without new data collection; that is you will create the most evidence-based criteria that you can, and that way, by this time next year, all of the AAPT articles will have been published, we hope.

Page 110

So that's one thing I'll put on the table because how we respond to that will sort of drive some of the other things we might talk about with research. So how does that sit with people?
Do any of the working groups feel uncomfortable about publishing things that they have confabulated without additional data?
DR. R. DWORKIN: I think the only clarification is, as I think we saw right before the break, some of the research that needs to be done is not going to take six months or maybe even a year to year and a half. It might take a couple of years.
We thought, rather than waiting for this AAPT effort, the initial AAPT effort to be complete with all new data collection underpinning it, which would be a three- or four-year process, let's do AAPT 1 as the most evidence-based criteria we can come up with, as Roger said, based on existing literature and reanalyses of data that we have access to, that's AAPT 1.
We could roll that out over the next 6 to

Page 111

12 months while at the same time Steve and the other members of the research committee will be getting the research going that will provide the basis for AAPT 2, that we would expect would appear in, I don't know, three years.
DR. FILLINGIM: Sam first, and then --
DR. S. DWORKIN: I think that is a fantastic idea, and I would from our experience encourage people not to be intimidated or reluctant to undertake such publications because they had few evidence-based criteria, but rather to distinguish in their publication the evidence-based criteria very clearly from the non-evidence-based because it will be a stimulus to research.
In addition to your research, there are other people out there -- some people in this room. There are other people out there looking for good ideas to do research on, and you'll be identifying a multitude of issues that are researchable. So I would encourage that. I think that's just a fantastic idea.
DR. FILLINGIM: Chris?

Page 112

DR. MIASKOWSKI: Chris Miaskowski. I also agree that it's a good idea, but I do have a question or maybe a point for consideration or clarification.
I was really intrigued with Steve's presentation yesterday, and I really like the methodology. I think the challenge for many of us -- and I can speak for the cancer pain group -- is that we don't have a gold standard. And so my question for us to consider is, is there an approach -- I'm not even sure it's a method -- that we should consider using, or trying to use, across these different pain conditions, rather than cancer say we're going to try this, and back pain says they're going to try this?
I ask the question, and I have no sense of the answer. But I'm wondering if it's something we should think a little bit about.
DR. BRUEHL: Yes. The short answer is yes, we should think about that. There are some -- there are certain conditions that it's easier to find a comparison group to do the kind of

Page 113

study I talked about than it is for others. So I think some of it is going to necessarily be dependent on the specifics of the condition and those comparators that are available.

For some conditions which may have a -- like the sickle cell pain group, where it's very difficult to find another condition that makes sense as differential diagnosis that we're going to try to distinguish between these two groups, we may have to use other approaches. And we may have to simply say for now we're not going to try to do the sensitivity and specificity, but rather focus on the internal validity and just getting the structure of it in a way that it fits with what we know about the existing literature.

An example that we brought up I think in one of the groups was if you've got a -- let's say we're trying to do a diabetic neuropathy and we're putting in the criteria that you have to have burning pain. And then we go and do research, and we ask in a systematic way about burning pain, and it turns out only 40 percent of the patients

Page 114

describe their pain as burning. We've got a disconnect between what the data say and what we've got in the criteria. That should require a change of the criteria.

It's very simple. I mean, this is not like high-level research, but that's the kind of thing that if we systematically collect those data sheets on signs and symptoms, we can go back and answer questions like that. That alone is advance beyond what we have now.

I think that's kind of what Sam's getting at, is don't be afraid just because there's nothing out there. Well, we can start with something. And the something is we do our best to put together some draft criteria -- and this is one thing I want to throw out, too, kind of in response to the previous question, which is there was a lot of variability across groups. Some of us had one or two things we're using to diagnose. Some had a laundry list of 10 things.

The truth is, none of us really know whether it should be 2 or 10 or what combination of those.

Page 115

The back pain group I think was brave enough to come right out and say we don't know, so we're not going to even bother to put them in there because we haven't done the research yet. That is theoretically legitimate.

Now, pragmatically, if we're trying to suggest some draft criteria to say this is the best we've got so far -- the back pain group I'll pick on you a little bit -- how do you want to handle that? Do you want to say we really don't know enough to even label things as likely neuropathic or nociceptive, so here's what we're going to recommend and here's why? So you don't really suggest criteria, but you say here's what the problem is based on our literature review. That might be acceptable.

Some of us clearly have done enough looking at the literature that we know it's possible to come up with some draft criteria that would at least make sense to a clinician, that you might be able to get some agreement on, even if the specifics aren't finely detailed. In that

Page 116

circumstance, I'm going to say go ahead and do it. Take your best shot at it. Suggest two of these symptoms and one of these signs and just go with it. And we'll test later on whether that is wrong, or we will seek to do that later on.

The question is, should you make them very stringent or relatively less stringent? Especially in a situation where it's going to be difficult to do the sensitivity and specificity research, you might want to set the bar a little lower so that you don't have to require as quite as many symptoms, so it's a little easier to get that diagnosis.

Anyway, I just wanted to throw all that out there. So it's going to vary from condition to condition. And talk with me about the specifics. I will be available as a kind of consultant on this stuff. I may or may not be able to give you better ideas, but at least we can talk about it and try to define how to handle this stuff.

DR. GEORGE: So the other implication of this is that that means there are going to be two

Page 117

research streams for pretty much all the working groups, one of analyses of existing data when such data exists, and that can begin quickly; and then the second stream of designing new studies to collect data that would answer the questions that we need answered and that aren't easily answered by existing literature or data. And so those two streams will happen in parallel. One will finish, as Roger said, over the next 6 to 9 months. The other could go on for three years.

DR. BRUEHL: John, did you have --

DR. MARKMAN: Just a quick question. Given that for some of these conditions like low back pain there's a wealth of clinical trial data and that ACTTION has access to some of those data sets through relationships with the sponsors, and/or FDA, or both, would it be possible potentially to use some of that existing data as part of the validation effort? If we're reanalyzing data, but for this new purpose, it might kind of what we're doing more compelling I think.

DR. R. DWORKIN: Our working group talked

Page 118

about getting raw data from Pfizer clinical trials. And as you know, there are a couple -- well, at least one lumbosacral radiculopathy clinical trial that Pfizer conducted of pregabalin, and then there are two or three trials that Lilly did of Cymbalta in axial low back pain. And I think it would be great to try and get those data and analyze them.

DR. MARKMAN: And some of the opioids, too. If we could pull that in, that would be great.

DR. ARNOLD: This is Lesley Arnold. Is there some danger or something we have to be careful about if we're putting out proposed criteria that people will start to use them [inaudible - intermittent mike] -- are now the accepted endorsed criteria. I'm a little concerned about that, especially since [inaudible] -- some criteria out there that we're actually challenging a little bit. And without data to support what we're saying, I'm a little hesitant to put it out there.

DR. BRUEHL: I have a little hesitation. And I will say with the CRPS, what happened was we

Page 119

kind of ran these criteria up the flagpole just to kind of see what they looked like and said here's a proposal for some research criteria. And we made very clear we weren't talking about using it for clinical purposes yet.

We didn't really have the intent of trying to change the way everybody did research, but what actually happened was many research groups, because they were desperate for a better way to diagnose it, picked up on it and started using it. Fortunately, when we replicated the validation study, it came out supporting them as being reasonably good.

I do think it is appropriate, in writing any articles at this stage, for us to say that we don't -- I mean, explicitly, it's like a cautionary paragraph that will be in every single article, "We do not recommend using this for routine clinical use yet. Possible use for research is up to the discretion of the researchers." The caveat is we have not yet validated X. I think that's appropriate to say that.

Page 120

DR. R. DWORKIN: Lesley, couldn't you also say that there are existing from Aberdeen that you would be able to analyze quickly?

DR. ARNOLD: Yes, we were going to do that, but that was just to help us better define chronic, widespread pain. But as far as putting forward the idea of widespread pain plus two symptoms, it's not yet -- that's never been proposed as a criteria for fibromyalgia.

DR. R. DWORKIN: But do the Aberdeen data have the symptom data also?

DR. FILLINGIM: Well, why don't we ask Gary?

DR. MACFARLANE: First of all, I would support Lesley's reticence because in fibromyalgia, we have a set of validated criteria. We have three sets of proposed criteria in the literature. And I worry a little about coming forward with a fourth set of proposed criteria without any data to back it up.

Having said that, in the fibromyalgia group, we felt that it was possible to move quite quickly. At Aberdeen, we're committed to doing some analysis

Page 121

of existing data that could help us finalize the study that we thought we needed to do in order to validate the criteria. Although a small amount of resources -- I think we're only talking about a small amount of resources, we felt that we could move fairly fast.

DR. R. DWORKIN: So the fibromyalgia group will do AAPT 1 and 2 at the same time, and then can begin working on AAPT 3 while we're still struggling with AAPT 2.

DR. BRUEHL: I think that it's important that we finesse this because we have to -- in anything we write about this, we have to make clear what the point of it is, which is for most chronic pain conditions, the diagnostic criteria have not been systematically validated in any way or subjected to any empirical tests. That is what we're trying to do, is to address the multitude of different diagnostic criteria and the absence of data to support them.

If you've got a situation with an accepted set of criteria like fibromyalgia and three

Page 122

different proposals already, I agree, putting a fourth proposal of what's unvalidated out there is probably not a great idea, but you might write about what the problem is and say we've got these three. These criteria don't match. They haven't considered X, Y, Z. This part has been validated. And then say this is why we're going to try to go this different approach, and then you've got data to support it. But I think we just need to be really clear in explaining in the text why it is we are even bothering to do this.

DR. ARNOLD: But I mean -- this is Lesley -- would you object to our being a little bit delayed in getting our paper out in the next year --

DR. BRUEHL: I don't.

DR. ARNOLD: -- if we could collect data within say --

DR. BRUEHL: Do it well, not fast.

DR. ARNOLD: So we could be one of the last to be published?

(Laughter.)

Page 123

DR. FILLINGIM: Yes. And that's what I was going to say, Lesley, is that the target would be to do the best you can as long as you can get the paper out in the next year-ish. If it's going to be three years, then that's a different story.

Sam?

DR. S. DWORKIN: I'd just like to add another level of emphasis and reiterate and support what Steve said, and then add another dimension; that is all those caveats clearly explicated, and a description of the mission of this ACTTION/AAPT thing, which is to promise reiterations so that in the next year, and the next year, you are promising to -- or that's your model system -- to undertake --

This is the initiation of a program of research and validation of the criteria. This is the first shot. It has all those caveats in it, and we will do the next sets, so then years 2 and 3 will be the next steps of what this group does. That will give your group a kind of leg-up on acceptability and respectability that is missing

Page 124

from when there are a bunch of people that have put together some diagnostic criteria for back pain or cancer or anything else.

Also, I don't know how -- Steve, I can't remember how you handled the sensitivity and specificity. You must have had control people.

DR. BRUEHL: Our controls were people with other kinds of neuropathic pain conditions --

DR. S. DWORKIN: Yes. So that's equally easy data to collect amongst multisite willing collaborators within the same condition to simply ask people who don't have the pain under consideration as a control group. And just make sure you have some number larger than the number of clinical subjects because you're doing mini or quasi-epidemiologic studies. And it's clearly that the first level of research that's needed are the epidemiologic studies.

What we did, we did a full-scale, major epidemiologic study eventually, and it wasn't very expensive, at least not at that time. But what it did was we could compare the data generated or our

Page 125

algorithm-generated diagnoses with the expert diagnoses and found, hey, these things, don't bother mentioning them. They never appear in our data. Nobody -- and the epidemiologic subjects don't have these kinds of things, like the burning symptoms that you talk about only occur. That eliminated for us occlusion, disc-joint noises. That's absolutely irrelevant because they were never associated with any pain.

DR. TURK: I'll just reinforce how you're talking.

DR. MIASKOWSKI: Chris Miaskowski again. Maybe this is a little naive as well, but I'm sitting here thinking across the presentations and thinking about a common yet perhaps disparate, differential, diagnostic taxonomy.

So that leads me to, is there -- should we be considering a common set of data elements? And if we believe that is the case -- so I'm going to use pain intensity because that's probably the simplest one. If we're all going to ask pain intensity, are we all going to ask it the same way?

Page 126

So that we have some reference point, if we're going to do function, are we going to consider maybe one common functional question? And I raise that as something -- I'd like to know the answer to that or maybe we derive that for 2.

DR. R. DWORKIN: So the answer is yes. So I think we've all thought -- when we've thought about the prospective research that we would be supporting, whether it was a small network -- for example, sickle cell pain -- of specialized sites, or whether it's a network that's going to do both spine pain and neuropathic pain and fibromyalgia because those are prevalent conditions, that there should be as much consistency in data collection as possible. I don't know how anyone could disagree with that.

DR. MIASKOWSKI: I'm saying we should do the same pain question for cancer pain.

DR. R. DWORKIN: Yes.

DR. MIASKOWSKI: And who's going to guide us on that? When are we going to get directions?

DR. R. DWORKIN: We have a research committee.

Page 127

DR. MIASKOWSKI: Okay. That wasn't clear.

DR. BRUEHL: So there are also things like allodynia that pop up again and again, so having a standard procedure we'll recommend for testing that, just operational definitions for things like that.

DR. MIASKOWSKI: You see that for phase 2.

DR. BRUEHL: Yes. I'm talking about --

DR. R. DWORKIN: The prospective research.

DR. BRUEHL: Yes. The retrospective, we're just going to have to use whatever was used.

DR. FILLINGIM: Ursula?

DR. WESSELMANN: The same question arises for collecting data on the comorbidities because the two large studies that are currently ongoing, the OPPERA study and the MAPP study, collect those data for specific pain syndromes, but the questionnaires they are using are slightly different. For example, for the pain syndrome that I have been studying for many years, vulvodynia, that has only been included more recently into some

Page 128

of the comorbidities.

So if we want to make this a large effort, then it would be good to have a very wide tool to collect it. But that would probably require a separate effort to collect this tool and then maybe to discuss what has worked better in the MAPP study, what has worked better in the OPPERA study, so that we don't have to start from scratch.

DR. R. DWORKIN: Questions like this are obviously is going to be something the research committee has to struggle with, how much time can we devote to collecting comprehensive data on comorbidities with keeping the study feasible in a pain clinic setting. I know we all are familiar with those research trade-offs.

DR. S. DWORKIN: I just have to encourage you to look at the research task force on back pain. It has a minimal data set, which will answer for many of the pain conditions and doesn't have stuff relevant to neuropathic pain. But for most of the common pain conditions is a very good research tool. And I wanted to throw out that it

Page 129

will be a part of all NIH studies funded for research on back pain.

So if you add that to what your effort would do, we'd have a much broader universe of people using a common set of pain measures and then modified uniquely for the conditions that the back pain put forth did not include in its minimal data set. And that applies to psychosocial, psychological status, functional status. Those questions will be virtually universal across all the pain conditions, and there's evidence already to show that impact, et cetera. It will be the same sets of questions -- could be the same sets of questions that are already used in research in similar ways.

So you could have one epidemiologic study that had an Axis 1 and an Axis 2 component, and the Axis 2 component contained all these questions common to the psychosocial domain, and the Axis 1 questions, batteries of questions, specific to each pain site. And the epidemiologic analysis would break those apart in one single, large-scale,

Page 130

epidemiologic study for the future. But a group like this could compel. That would be a very compelling and powerful study.

DR. TURK: Let me amplify that, if I will, because by disclosure I was on that task force. And one of the things that we wrestled with was how to get this to be used in the real world versus just the clinic. So we made every effort we could to have the smallest number of questions that we thought were appropriate.

Now, obviously, it was for back pain, so there are some things that are unique. But at least the research committee could begin there, look at what we did, and then see what if anything we want to modify. But just so you know, there was a major effort to make sure that we kept this as short and as simple because we wanted surgeons to use it in their general practice and all types of circumstances. So there are some precedence to help us get started on that.

DR. S. DWORKIN: Also, that it's suitable for clinical research in clinical settings and

Page 131

epidemiologic research, so that both domains of research enterprise generate the same set of basic questions.

DR. FILLINGIM: Other questions? Comments?

(No response.)

DR. TURK: Why don't we try to wind up with sort of going-forward steps and how we're going to help and keep the energy going over time?

DR. BRUEHL: I have the solution to this problem

(Laughter.)

DR. S. DWORKIN: He's smarter than you. He asked the question first.

(Laughter.)

DR. BRUEHL: Yes. I think most of you got the idea that what we need concrete out of this is a couple of things. One would be ideally a draft set of criteria. Now, you may elect not to publish that right away. That's okay. But a draft set of criteria, your best shot, and then a form, which parallels what I showed up on the screen for the CRPS database that just has the basic information

Page 132

you would want to collect in a clinical setting on each patient.

I agree that starting out with -- like this back pain task force is a way to identify an ideal way of asking certain questions. We can add to that different conditions. There may be certain things that aren't covered. Like the neuropathic questions may not be adequate, so maybe we need to operationally define testing allodynia, hyperalgesia, and things like that.

But we'll try to come up, I think, with a common set of ways of assessing all those key characteristics. And then each group is going to be tasked with -- each task has to put together those into what they think should be on their database form that they're going to use for their area. And as much as possible, we want to have similar wording -- or identical, ideally, wording across groups for similar concepts.

So we need the draft criteria. We need a data form. The research committee -- and I would I guess be the point man on that for contacting me if

Page 133

you have questions. I'll try to help you with that. If it's a question that is more complicated, we'll probably have a discussion on the phone as a committee about these things. And anything that is going to affect multiple groups, we may respond, I would assume, to all the groups to say this question's been asked by this group. All of you from now on do it this way, to try to keep some consistency.

DR. R. DWORKIN: So Steve, you're referring to the prospective research.

DR. BRUEHL: Yes.

DR. R. DWORKIN: Right. All I would add to that is you should also be thinking of whether there are literature reviews, systematic reviews of the literature, that would help your working group that can get started right away. And we can provide modest honoraria for a fellow or a graduate student or a junior faculty member if you need a systematic literature review done. So that's one thing that can get started right away that isn't directly related to the prospective research.

Page 134

The other thing that of course we've mentioned is studies of existing databases. So let us know if we can help you either identify existing databases, kind of negotiating with pharmaceutical companies who have clinical trials, or whether, again, modest financial support would allow you to begin an analysis of existing data quickly.

So those are two types of help that would occur before what Steve was talking about, which is the prospective research. So just get in touch with us about any of those needs.

DR. BRUEHL: I just want to mention, I'm not going to be a control freak about the analyses. You are welcome -- if you have some idea of how you want to proceed with analyzing this stuff, if you get access to databases, go for it. I'm willing to help if I can and if you want me to. But by all means go do it on your own if you feel capable of doing that.

I mean, a lot of these things are going to be self-evident. And a lot of the questions you can ask and the answers you can get will be pretty

Page 135

obvious once you see the way the data are laid out and you know what you're looking for.

DR. PAICE: This is Judy Paice. Steve just raised an interesting point. For AAPT 1, are you going to want to look at all of our draft criteria so that you will standardize some of the terminology?

DR. BRUEHL: That was something we hadn't addressed yet. And I think we should probably talk about that and maybe get back to you. I think it would make some sense for all of you to send your best version of your draft by -- and we'll have to set a deadline. But give that to us so we can take a look at it. I'm not sure if we're going to do an editing process or not.

DR. R. DWORKIN: So this is an important point. Someone who isn't here now, because he had to leave early, relayed a message to us that he thought one of the real strengths of this effort will be the consistency in how the diagnostic criteria and information is laid out across conditions. And so I think that point is very well

Page 136

taken. And we want to do everything possible, Judy, so that the cancer pain article and chapter look kind of similar to the neuropathic pain chapter and the back pain chapter.

So the kind of specific ways in which the boxes are filled are going to be different, but I think the structure, the approach, should be as consistent as possible.

DR. PAICE: I'm even thinking -- the papers, that's very helpful, too. I'm even thinking about the actual criteria. Some of the words we're using, we're using different words for paresthesias or dysesthesias.

DR. BRUEHL: Yes. Think about the DSM model. If you go look at the DSM, it's very consistent from disorder to disorder in terms of how they word things.

DR. R. DWORKIN: And it's got a glossary.

DR. BRUEHL: Yes. And I think we would want to do the same thing, operational definitions very clearly defined and similar wording. But we don't have to worry about now. We can come back and edit

that to improve the consistency. The first step is just to get kind of laid down what the concepts are and what you think the criteria should be, and then we'll I guess take a look at it and maybe give feedback.

Adjournment

DR. FILLINGIM: Okay. And with that, we're done. Thank you all very much.

(Applause.)

DR. TURK: We're beginning. We're not done.

(Laughter.)

(Whereupon, at 3:57 p.m., the meeting was adjourned.)

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