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(8:00 a.m.)

DR. KATZ: Good morning, everyone. For those of you that I don't know, which I think there are very few of you, my name is Nathaniel Katz. I have a very easy and pleasant job this morning, which is to introduce some of my favorite people who are speakers this morning, and I would like to begin with Dr. Srinivasa Raja.

Where are you, Raj? There you are. Everybody I think knows Raj. He's been one of the most longstanding and prolific contributors to the pain field, I would say, someone who I've had the pleasure of learning a great deal from over the years and counting as a professional friend. He'll be speaking to us, introducing the first session.

Thank you, Raj.

Presentation - Srinivasa Raja

DR. RAJA: Good morning. Yesterday, we started with an incredible journey, almost a full decade journey from the start of the reports of central sensitization to 2019, where we...
have these clinical pain syndromes and overlapping pain conditions.
The task I was given was a simple task of summarizing all of this work and coming up with a design for a clinical study in the next 45 minutes. (Laughter.)

DR. RAJA: When Bob or Dennis sends me an email or asks me to talk at this meeting, I usually say yes because I think of it as an exercise for my aging brain. (Laughter.)

DR. KATZ: Then, as I started researching this area and figuring out what I should be saying and summarizing some of this work, I started getting a little worried because I thought I was seeing signs of the shrinking of that brain, especially in the prefrontal cortex and maybe in the hippocampal regions, because I ended up having more questions than answers. Fortunately for me, I had Helen Keller who was comforting me by telling me that it's okay to have questions. When you have these kinds of questions, then you say how do you go about talking to this erudite audience? So like Charlie, I kind of asked Lucy for some advice, and Lucy gave me this advice. "If life seems to have more questions than answers, try to be the one who asks the questions." (Laughter.)

DR. RAJA: So I think in my presentations, I will provide some perspective, but I also will be asking quite a few questions, hoping that the collective expertise here will answer those questions.

We heard this phrase from Clifford yesterday, "What's in the name?" And I think I have to differ from Shakespeare who said, "A rose by any other name would smell as sweet." So maybe it's true for a rose, but in researching this topic that we're discussing in the last 24 hours, what I came across is this list of names for this condition. This is not an extensive list. It's central sensitivity syndrome; centralized chronic pain; overlapping chronic pain conditions; chronic widespread; chronic primary pain; fibromyalgia-ness; nociplastic pain; and many more. Looking at Steve, I feel like we are in this field where CRPS was more than two decades ago, before things like reflex sympathetic dystrophy, causalgia, Sudeck's atrophy, et cetera, and a single name came up for that. So I think the first thing is the name does matter, and if different specialties refer to those conditions by different names, I think the field will take a lot more longer to progress.

What are you talking about? Is this a condition? Is this a disease? Is it a disorder? Is this a syndrome? Each of those have special meanings. I personally thing that we are dealing with a syndrome, a collection of signs or symptoms that characterize or suggest a particular disease. You also heard from Roger and several others that this central sensitization has maybe associate overlapping pain conditions. If there's one thing during my long association with Bob Dworkin, that is if you need to make an impact in a field, you have to have an appropriate acronym. And that acronym should have at least a word that has some action in it, and it has to have one or more letters that are replicated or duplicated, and it's better if you have a logo that goes with it.

So here's my suggestion, CCOPSS or chronic centralized overlapping pain sensitization syndromes -- and here's the logo that goes with that.

IMMPACT meeting? What prompted Bob to say that we need to have a 2-day session to consider these conditions such as central sensitization and some somatosensory amplification? One hypothesis I had was maybe there is possibly a central common mechanism for these conditions that is different from acute or chronic thing conditions such as inflammatory on neuropathic pain states. So maybe the central sensitization that occurs in these
1 disorders is different from the central
d 2 sensitization which we know occurs after
  3 inflammation or after neuropathic pain. There's
  4 some suggestion, based on twin studies, that they
  5 may be a greater genetic influence for these
  6 chronic overlapping conditions.
  7 An inference of that is that treatment
  8 effectiveness in central sensitization syndromes
  9 may be unique and may be different from other
 10 chronic pain conditions. And hence, if you want to
 11 design a study, it should be appropriate for those
 12 therapies.
  13 I've long been interested in neuropathic
  14 pain, that's been married, and the poster child for
  15 the central sensitization syndrome is fibromyalgia.
  16 I started by looking at are there differences in
  17 terms of drugs that work for these two conditions?
  18 As you've already heard, partly yesterday,
  19 the FDA approved drugs for fibromyalgia,
  20 duloxetine, pregabalin, and milnacipran, and they
  21 are also approved for neuropathic pain states such
  22 as diabetic neuropathy, chronic musculoskeletal
  23 pain; and in terms of pregabalin for diabetic
  24 neuropathy, postherpetic neuralgia and spinal cord
  25 injury pain. Although milnacipran, I couldn't find
  26 a study that's specifically looking at neuropathic
  27 pain, at least preclinical studies seem to suggest
  28 it's effective in neuropathic pain states as well.
  29 We also heard about other drugs or
  30 treatments such as ketamine infusions, which work
  31 in about 60 percent of fibromyalgia patients but is
  32 also effective in neuropathic pain patients, and
  33 studies to show that CBT is also effective in
  34 fibromyalgia and neuropathic pain and
  35 osteoarthritis. Drugs that are not effective in
  36 neuropathic pain states are also not useful in
  37 fibromyalgia. An example is NSAIDs, and the
  38 Cochrane review suggests that NSAIDs are not
  39 effective in treatment of fibromyalgia.
  40 Here are the treatments that are effective
  41 for neuropathic pain and are also effective for the
  42 poster child condition, fibromyalgia. One can say
  43 maybe the drug response or dose-response curves for
  44 these two conditions may be different. Thanks to
  45 1 Lesley, we have this study where she looked at
  46 studies of a single drug, pregabalin, post-diabetic
  47 neuropathic pain, postherpetic neuralgia, and
  48 fibromyalgia, and this shows the global impression
  49 of change is fairly similar in PHN and fibromyalgia
  50 in terms of percent responders. Also, the change
  51 in sleep quality is similarly effective in both
  52 neuropathic pain states and fibromyalgia.
  53 One can then ask the question, is this
  54 primarily an issue of assay sensitivity. The trial
  55 designs are not sensitive enough to differentiate
  56 central sensitization from other conditions such as
  57 neuropathic pain?
  58 We've talked about this amplification that
  59 occurs in central sensitization and is there
  60 difference between neuropathic pain and other
  61 central sensitization syndromes, nearly an extent
  62 of the magnitude of the amplification or the extent
  63 anatomically in terms of where the amplification
  64 occurs, such that in post-op pain, maybe the
  65 amplifier is turned on slightly, in neuropathic
  66 pain, a little bit more, and central sensitization
  67 or fibromyalgia, it is set to a maximum.
  68 An ultimate explanation may be there's a
  69 totally different mechanism for the central
  70 sensitization that occurs in neuropathic pain
  71 versus the central sensitization syndromes such as
  72 chronic overlapping pain conditions.
  73 In developing a clinical study, the basics
  74 of it is to define the population that you're
  75 interested in, which is the reference population.
  76 You have an objective or a primary question that
  77 you're interested in. Design the study by picking
  78 a study population, including inclusion/exclusion
  79 criteria, and then figure out the outcome measures
  80 you'd be interested in.
  81 If you have it in a tabulated format, what I
  82 hope to do is to pick certain aspects of this
  83 one-on-one study design, that is what should be the
  84 reference population and what should be the study
  85 population; how do they allocate randomly; and
  86 maybe the assessment outcome measures.
  87 What should be the reference population for
  88 central sensitization and centralized pain? One
We talked about quite a bit yesterday as to some of the mechanisms that may be involved. For instance, it's clear from some recent studies that not all patients with central sensitization have centralized pain. This is a study from Staud, where they did pressure pain thresholds, injected some local anesthetic lidocaine into a muscle, the deltoid, where they were looking at pressure pain thresholds.

They were comparing normal subjects with patients with fibromyalgia, and obviously they showed that the pressure pain thresholds were lower in the fibromyalgia patients. But when they injected the lidocaine and tested both the sites where it was injected or the muscle that was injected, as well as broadly across other muscle populations, they found that there was an increase both at the site as well as peripherally. So that suggests that at least in a subset of patients of fibromyalgia, the periphery seems to have played a role.

A study that was just published in this issue of Pain from a Danish group, looks at phantom pain and neuropathic pain states, and looked at peripheral nerve block, and showed that a significant portion of those patients, their pain was reduced significantly, complete and a good relief from a local anesthetic peripheral block, again suggesting in neuropathic pain states as well a subset of patients have an afferent drive that is important role.

We talked about certain mechanistic specificity, based on purely clinical features. Which are rapid screening tools for fibromyalgia. Then we are left with some screening tools, talking much more on that in the next presentation. Neuroimaging because my colleague Claudia will be looking into subgroups of patients, so we'll come to this. We also talked about certain mechanistic neurobiological correlates such as increased gain in the somatosensory system, exemplified by allodynia, hyperalgesia, temporal summation, and wind-up, and reflects nociceptive thresholds or objective markers as Vitaly talked about, such as neuroimaging.

In response to a question that my kids usually used to ask when we were on long drives, "Are we there yet?" the answer I heard was not yet, "We're never there yet!" The lumpers may say that the patients with centralized pain may differ in their drug response compared to those where the peripheral drive has an important role. Some of those would say that the fibromyalgia phenotypes, whether it's top-down or bottom-up, may differ in the therapeutic responses.

So the question that you may ask and the population that you may study may vary depending on the type of questions that you're interested in. So what should be the study population, then? We said the broad clinical features were widespread pain and multisensory hypersensitivity, but other conditions such as fatigue affect, liability, changes in mood, sleep disturbances, cognitive disturbed problems; how many of these features do you need and what is the sensitivity and specificity, based on purely clinical features.

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Three of the tools that have been in the literature, one is a FibroDetect from the German group. Ralf Baron's group is kind of a modification of the NeuroDetect, and then Lesley's fibromyalgia diagnostic screen, I'm going to let her talk about that because I'm sure she knows more than I do, and then the fibromyalgia Rapid Screen tool.

The FibroDetect was started with about 14 questions, and then it was pared down to about 7 questions, and the total scores ranged from 0 to 9. It's kind of yes/no answers. If the score was over 6, then the sensitivity and specificity for fibromyalgia was about 77 percent.

The FiRST, or the Fibromyalgia Rapid Screen tool is, again, a self-administered tool with 6 questions; again, yes/no answers. A score of 5 or more had a high sensitivity for fibromyalgia.

This was compared with either the ACR-90 diagnostic tool or how clinicians diagnose these patients. And again, these tools had sensitivity of 76 percent and specificity around 80 percent or so.

These could be rapid screening tools for fibromyalgia, but the question is, are these tools specific to fibromyalgia or are they generic enough to detect other central sensitization conditions and/or chronic overlapping pain conditions? The answer I think is, as far as I know, they're more specific to fibromyalgia and may not be useful for other conditions.

Then we are left with some screening tools that are more specific for central sensitization. Obviously clinically, there is widespread unpleasant experiences that is disproportionate to any observable peripheral cause. Three of the screening tools that have been used are the Pain Sensitivity Questionnaire, the Central Sensitization Inventory, and the Sensory Hypersensitivity Scale. Of these, the Central Sensitization Inventory has been studied widely and used in the literature. I am searching the NIH sites. I scan across another tool, a centralized pain index that was part of an aim for an NIH grant, and Dan may be able to tell us later because he's the PI on that grant, which is partly aimed at constructing a centralized pain index.

What is the Central Sensitization Inventory? It identifies key symptoms associated with central sensitization. It consists of 25 questions related to current health symptoms, and each symptom's item is measured on a 0 to 4 Likert scale, so we would have a total score of 100 at the maximum. It's been validated for fibromyalgia, chronic widespread pain, chronic low back pain, and compared with normal subjects. What you see in the scale from this study by Mayer, et al. is that normal subjects, or even patients with low back pain, have a scoring of around 40 or less, and patients who are with fibromyalgia had scores of around 60 or so. That seems to be inventory that suggests, or at least goes along with, patients with more widespread pain.

The other hypersensitivity scale that is considered to be an index of sensory hypersensitivity looks not only at pain but also a variety of stimuli such as taste, light, touch, smell, allergies, heat and cold. What they showed is, again, it's a 25-items measure, and it's a human factorial measure of sensory hypersensitivity. It's shown to have some modest association with three quantitative sensory testing measures such as heat threshold and tolerance, as well as cold tolerance. The fibromyalgia subjects scored higher than patients with low back pain, or osteoarthritis, or controlled subjects. This sensory hypersensitivity scale, unfortunately, also correlated with symptoms of depression and anxiety. Whether this is unique for the aspect of central sensitization or it shows other factors such as symptoms and depression, as well as anxiety, is unclear to me at this stage.

Based on a consensus panel of sorts, Europe recommended the following criteria for diagnosis of central sensitization from muscle disorders or musculoskeletal pain; that is if the pain is...
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1 disproportionate to, quote/unquote, “the pain experience,” and if it has a diffuse pain distribution, then these patients have central sensitization. If they don’t have both of those 5 but yet have a score greater than 40 on the Central Sensitization Inventory, or CSI, then they still may be having central sensitization. This was by Nijss, et al.

Subsequently, Williams modified this a bit and says it should be a diagnosis of exclusion.

You rule out neuropathic pain, you rule out nociceptive pain, and then if the pain experience is disproportionate to the nature or the extent of the injury and has a diffused distribution, and they meet criteria 1 to 3, then they have central sensitization. Or if they meet 1 and 2, that is they don’t have neuropathic pain, they don’t have inflammatory pain, but they have this general hypersensitivity to sensory stimuli that still could fit into this central sensitization group.

The pros and cons of these self-assessment tools, obviously they’re practical, they are easy to administer, and they have been validated comparing other conditions to fibromyalgia.

However, the cons are that they have not been tested carefully in terms of how they correlate with objective measures, such as measures of temporal summation, central pain modulations, or even neuroimaging.

The other question is, are these measures to specific for fibromyalgia and not generic enough for other chronic overlapping pain conditions? I think these are things that we need to discuss.

We talked in terms of objective biomarkers. We talked about the role of quantitative sensory testing and imaging, and those, as far as I know, are not useful as diagnostic tools. But just for completeness sake, I wanted to also indicate that studies have shown in patients with fibromyalgia, there is an increase in pain facilitating neurotransmitters such as NPY, CRS, Substance P, BDNF, and even inflammatory biomarkers such as cytokines, IL-6, IL-8, and IL-1 beta, and TNF alpha.

So in patients with central sensitization of fibromyalgia, some of these biomarkers are enhanced. That is pain facilitating biomarkers or neurotransmitters, why there is a decreased production of inhibitory transmitters such as 5HT dopamine and beta endorphins, so something to consider. Again, the sensitivity and specificity of these as a diagnostic tool in a given patient is not known first.

I came in searching for this. I came across an article in a journal that I do normally read, the Journal of Biological Chemistry, but it tweaked my interest because it talked about a chemical fingerprint for fibromyalgia. It tweaked my interest even further because the diagnostic tool is based on a phenomena called Raman scatter, which is based on a discovery that was made by an Indian physicist who was the first Indian physicist to get the Nobel Prize in 1930, and he was knighted by the Britishers of that time.

This Raman scatter is actually when a indirect light hits an object, obviously the light scatters, and that is relevant as the initial light. But there are other smaller, less abundant scatters that are light, which he discovered known as the Raman scatter. In this particular study, a single dried blood spot from a finger stick was analyzed from patients with fibromyalgia, and it showed specific microspectroscopic signals, or peaks, as well as some infrared peaks. Then these peaks that were seen in patients with fibromyalgia were compared with patients with SLE, or lupus erythematosus, and with rheumatoid arthritis.

Using the combination of the Raman spectroscope as well as the infrared spectroscope, there were clear patterns that could be shown that could separate patients with fibromyalgia from rheumatoid arthritis, as well as SLE. And more interestingly, apart from the fact this is a single blood stick that has a metabolic fingerprint, what they showed was, in an interesting analysis, that the changes that they observed in the spectrocope correlated with self-reported disease activities, or symptoms, as determined by the FIQR score, which
is a Revised Fibromyalgia Impact Questionnaire. So here is a tool that not only can diagnose this condition but also correlate symptomatically with a degree of symptoms. So maybe we'll find out whether it comes out as a tool in the future.

The other question that comes to mind, we had some discussions yesterday, the question of whether we should include or exclude in a study patients with multiple comorbidities such as fatigue, mood disturbances, sleep disturbances, and cognitive changes.

If you are a lumper, you might say that this is part and parcel of fibromyalgia, and they may have a shared mechanism or it's secondary to a consequence of the widespread pain, and that pain relief will also result in improvement of these different factors. If you're prone to be a splitter, you might say this may confound your results, and the interpretation of the results may be difficult.

In the drug study pregabalin in fibromyalgia patients, many of these patients also had osteoarthritis, and Charles Argoff did some retrospective analyses on these studies, whereas some patients with fibromyalgia also had osteoarthritis, and looked at dose-response curves, and clearly showed that regardless of all the patients with osteoarthritis or not, the pregabalin was effective in reducing the pain of fibromyalgia. But the more relevant question that was unanswered is what was the effect of the treatment of pregabalin on the osteoarthritic pain in these patients with fibromyalgia? So you don't know from the study if the drug equally is a factor in treating fibromyalgia, and also a factor in treating the osteoarthritis.

The other aspect is that the patients with fibromyalgia are a heterogeneous group. In this study, it looked at more than 1200 patients with fibromyalgia and classified them using cluster analysis into 5 different clusters. Cluster 1 is those who had high pain and severe mental and physical impairment. Cluster 2 had high pain but predominantly physical impairment. There were other clusters where there were more mental impairment and less pain.

Then they looked at the efficacy of duloxetine in these different clusters, and the bottom line is that the mental impairment, based on the scales they used, was most attuned to comorbidity, and it influenced the outcome of the drug therapy compared to physical impairment. The better treatment effect of duloxetine they observed are those who had physical impairment and high pain, but not necessarily the high mental impairment.

So the reason for bringing this study is just to say that, fibromyalgia, there are different clusters and there are different degrees of physical and mental impairment, and the efficacy of a drug may vary depending on the complexity of these different conditions.

When we go into a clinical trial, we randomize patients. Sometimes we just do simple randomizations where the whole sample is then distributed into equal groups, a treatment group or a placebo group. If there are subtypes or strata, then the population may be divided into subgroups, and then the randomization occurs within each subgroup.

Given the complexity of these central sensitization conditions, my suggestion is to be able to get meaningful information, that we may have to stratify these patients and use the proportional stratified random sampling tool. And the pros of such a strategy would be that it accurately will reflect and represent the population of patients that we are studying, that it will have greater position and may require a smaller sample size and may save money, and may allow us to do subgroup analysis subsequently.

The cons obviously are defining the strata is critical. It requires the ability to classify our patients into subgroups a priori before we randomize those patients. Therefore, it could be more complex to organize, and the analysis may be somewhat more challenging.

The more important question that we may have
to decide is if we stratify, what are the relevant strata? Should it be those patients who are predominantly a single primary pain pathology or multiple pain conditions? Are these patients who have predominantly, quote/unquote, "centralized pain" where the periphery contributes less to their overall pain or is it a combination of both peripheral and central mechanisms?

These patients who have comorbidities, is it the degree of physical versus psychological features? One would have to then appropriately power these to determine differences across the strata.

In any study, you have a primary question that you are interested in answering. I can think of two questions here. One, is drug A effective in patients with central sensitization syndrome regardless of their primary pain presentation? So regardless of where they are, irritable bowel syndrome, or fibromyalgia, or osteoarthritis, is the drug equally effective across conditions where there is central sensitization?

The second question could be, drug B, does it help understand the neurobiology of central sensitization? That is, are the mechanisms of central sensitization different from neuropathic pain? Does this drug work specifically on those patients who have central sensitization that is different or somewhat unique in some way compared to other conditions such as neuropathic pain?

To answer question A, you may enroll all patients with central sensitization regardless of their primary pain pathology and presentation and study the efficacy of the drug at multiple pain sites.

For question B, you may enroll all patients with central sensitization, but stratify them based on whether there is solitary or multiple pains and compare these patients with a patient group of neuropathic pain states so you can do a comparison of whether these drugs are better or more effective in central sensitization conditions compared to neuropathic pain.

So we've talked about study designs primarily from a perspective of randomized control trials. I liked the cartoon that says, "Do you know about any RCTs that provide evidence that we should use RCTs?" The question, in looking at people who know more about clinical trial designs than I do, I came across these two cohorts that carefully conducted observational studies may provide more evidence than poor RCTs.

Unfortunately, a perfect trial can only exist in our imagination. Maybe RCTs may not be the best or only solution, and maybe a multicenter trial with large registries of patients may be also a useful tool in studying the central sensitization syndromes.

What are the outcome measures that we should be studying in these patients? Obviously, a long time back, the IMMPACT II suggested 6 core outcome domains such as pain, physical functioning, emotional functioning, global impression of change, symptoms and adverse events, and participant disposition.

These are appropriate for studies in central sensitization, as for any other pain condition.

The other outcome measure that's been used in fibromyalgia studies, particularly -- and I know Ian and Lesley had used it in some of their studies -- is the Fibromyalgia Impact Questionnaire, which I'll talk about in the next slide. Others have talked about symptom clusters, and obviously other measures could be QST measures such as temporal summation and CPM, or conditioned pain modulation, imaging, and other biomarkers.

So these could all be outcome measures. At this stage, I'm going to just touch on the IMPACT questionnaire. This was initially brought about in the end of the last century, but then revised subsequently. It consisted of 21 questions, and it was shown that it could separate fibromyalgia patients from rheumatoid arthritis, SLE, or healthy controls.

Subsequently, in the revision, there were four other new symptom measures that were introduced such as memory, tenderness, balance, and sensitivity. There are 21 items across the
 domains. Patients can complete in less than a
2 minute and a half. The total score of 0 to 39 was
3 a mild effect; greater than 39 was moderate; and
4 greater than 60 was a severe effect, so in terms of
5 impact of the fibromyalgia. Minimally, clinically
6 important differences could be detected by a change
7 in score of about 14 percent.
8 Here’s just an example of a study that just
9 came out two or three years ago, looking at an
10 antidepressant in fibromyalgia patients. This
11 study was done in Japan, and they did a Japanese
12 version of the score, and again shows a reduction
13 in their pain, the change in numerical ratings
14 scores, and that corresponded with the change in
15 scores in the Japanese version of the FIQ. So
16 again, this could be an outcome measure that one
17 could use in some of these patients.
18 People have talked about using clusters of
19 symptoms such as the SPADE and the SPACE, and in
20 oncology patients, the PSF. SPADE is basically
21 sleep disturbances, pain, anxiety, depression, low
22 energy, and fatigue. There are variations of

1 conditioned pain modulation in patients with
2 fibromyalgia. What the studies showed in the left
3 is that treatment with tapentadol resulted in a
4 decrease in pain compared to the placebo group,
5 which is in red, and that the responders were also
6 higher in the tapentadol group in the green versus
7 the red.
8 They also showed that there was a change in
9 conditioned pain modulation that the tapentadol
10 group in contrast to the placebo significantly
11 increased the defending inhibitory pain pathway or
12 the conditioned pain modulation. A treatment
13 resulted in change in conditioned pain modulation.
14 The study is more relevant, or important,
15 because they also did something, a measure using
16 cranial confocal microscopy. They measured
17 neurofiber length, neurofiber density, and no
18 branching in the cornea. And if two of those three
19 parameters were abnormal, then they would say
20 that’s an abnormal finding.
21 The interesting observation here was when
22 they compared the drug effects on conditioned pain

1 these. The suggestion is that one should not be
2 focusing just on pain, but should have other
3 measures that capture the full symptom presentation
4 of these patients with central sensitization
5 conditions.
6 Sleep is an important measure, the study
7 looks at what should be the appropriate sleep
8 measured. What should be the scale? How do we
9 detect sleep disturbances? Normally sleep diaries
10 have been used. Others have used act, actigraphy
11 or polysomnography. This study compared the
12 effects of, in this case, and intervention CBT on
13 sleep measures in fibromyalgia patients.
14 The conclusion is that although actigraphy
15 was most sensitive in some respects, some aspects
16 of it, sleep diaries captured the greatest
17 improvement in all parameters. So a sleep diary
18 seems to be sensitive enough to detect differences
19 with the treatment.
20 A study that was just in press, and hasn’t
21 been published in European Journal of Pain, looked
22 at the role of tapentadol and its effects on
optimization, and then the patients, with a certain criteria in this case, and 50 percent or greater response are randomized, and when you have a double-blind phase of 13 weeks. The primary endpoint, then, is the time to loss of therapeutic response.

Between these two studies, one study in postherpetic neuralgia and the other in fibromyalgia, again, the final endpoint or the most important that they checked was the median time to loss of therapeutic response.

Here are the data from these two studies. Apart from Lesley, anybody want to guess which was the fibromyalgia study? Was that on the left or the right? Any guesses?

(No response.)

DR. RAJA: Okay. So here's the answer. The left was the fibromyalgia patients; the right is the postherpetic neuralgia. The difference, one thing I want to point out is that the left is from 1 to 0. The scale is different from 1 to 0.5, and if you look at the difference between these two studies in terms of the treatment group, as well as the placebo group, the difference is almost the same 16.8 across the 13th week, which is the endpoint.

But look at the two studies and how different they are in the sense that at a 30-day period, in the PHN study, almost 85 percent of patients, when they were taking placebo, were still, quote/unquote, "not withdrawing from the drug," or still had some kind of response. In the other study, at 30 days, only 45 percent of the patients had some degree of response; so again, same drug, two studies, PHN. So one has to take into consideration the different responses across different patient populations, and then design the studies appropriately.

To summarize, what I want to point out is that one of the first orders of business may be to come up with a consensus on the name and the diagnostic criteria for the condition we've been talking about for the last day and a half. In defining the study population, at this stage, we are left with some self-assessment tools, maybe such as the Central Sensitization Inventory or the sensory scales, that the objective measures of central sensitization are not useful for clinical studies at this stage. The spectroscopic fingerprints may be a potential tool in the future. Depending on whether you are a lumper or a splitter, the study question of interest may be different; whether you're interested in the neurobiology of the disease and was there treatment efficacy across a heterogeneous population; that is, are we talking about efficacy versus effectiveness across a broader population?

The study designs should probably use some form of stratification for better understanding of where there is a shared mechanism across these different central sensitization conditions, and that outcome measures, apart from the impact measures, measures such as the Fibromyalgia Inventory Questionnaire, the revised one, or other outcome measures may be more appropriate, and we'll probably hear a little bit more of that from Claudia in the next presentation.

I want to thank you all for your time and allowing me to reflect on this issue, and hopefully this will help steer some discussions in the coming time period. Thank you very much.

(Applause.)

DR. KATZ: Thank you very much, Raj. I think we're going right into the next presentation because we're running slightly behind on time, and we have lots of time for discussion both after the next few presentations, and then as well as all afternoon.

With that, I'd like to introduce Claudia Campbell, who's also from Johns Hopkins University for the next presentation.

Presentation - Claudia Campbell

DR. CAMPBELL: Good morning. As the last speaker today, you would think that I would summarize all of the great talks we've had so far, but I decided not to do that. Instead, I'm going to try to split some hairs and pick up some threads from previous conversations.
I have to admit that I was not super familiar with the term "somatosensory amplification," which is in my title. So my first order of business was trying to figure out the distinction between central sensitization and what this somatosensory amplification really means.

Then also, if I was planning a clinical trial, what kind of advice would I seek from a group like this to try to help me do a good one?

When we talk about somatosensory amplification and central sensitization, are we talking about this kind of overlap or more like this kind of overlap? What are we really getting at here? You don't need me to give you the definition of central sensitization; we've been talking a lot about that. It is awfully handy that the IASP has a nice taxonomy on that. It does not for somatosensory amplification.

I went looking at Wikipedia of course, but started to wonder, hey, is somatosensory amplification sort of like allodynia and hyperalgesia, but for non-pain; just for everything? It does appear to have central and peripheral somatosensory nervous system components. Somebody summed it up as heightened awareness of and attention to internal sensations and symptoms. So I started thinking the overlap is probably in the space of central pain-specific somatosensory amplification, and maybe that's what central sensitization is.

Like Rob, I went to PubMed, and I did not put "pain" in my search term, which would have been much wiser. I just looked up somatosensory amplification and came up with 200-ish different articles, and in perusing those, it does appear like this somatosensory amplification is associated with a number of physiological phenomena like EEG and different ways to get at sensitivity. It's also associated with -- well, I'm going to talk a little bit more about QST in a moment -- a pain modulatory profile. It seems like this area might be where they overlap.

Several people have mentioned all of the different terms people use to try to understand these different phenomena. And while there were only about 200-ish for this specific somatosensory amplification, somewhere over 2,000 came in for sensory processing, sensitivity, sensory overresponsiveness, sensory alteration, and Raj and Rob both described all of the different terms we use to get at these overlapping or same constructs. So I'm going to keep trying to come back to the goal of my talk is supposed to be implications for clinical trials. I keep wandering off of that specific topic. But it does seem like there have been recent studies trying to understand how somatosensory amplification and central sensitization are associated.

This was an interesting systematic review that came out just a couple of years ago that found this general sensitivity, whatever we're going to call it, was the strongest predictor of altered central pain modulation in chronic musculoskeletal pain conditions. So it makes one wonder like maybe this set of sensitivity precedes this more centralized pain-focused sensitivity.
were vastly more likely to develop TMD and other global symptoms. So they've got all this stuff. Not surprisingly, those folks had the most pain and the worst disability with their musculoskeletal symptoms as opposed to those in the adaptive cluster, which were characterized more by higher prevalence and healthy folks and less pain. Interestingly, there is another cluster, the pain sensitive cluster. They had the highest QST findings, but not as high on the psychosocial and physiological symptoms as I might have suspected. The terms seem different. How might we measure one versus the other, and do we really need to measure them both? It feels obligatory to say something about chicken and egg which comes first. There has been quite a bit of discussion about that here. The literature seems fairly convincing that psychobehavioral factors do seem to contribute to the risk of developing pain and likely maintaining it.

OPPERA and other studies, there's been well over two dozen QST studies looking at postoperative pain and trying to understand how those physiological alterations might predict the development of pain, while other studies have challenged that idea and say that, well, these variables, and how those factors are associated with their clinical findings are different. Almeida and colleagues did something similar with pressure pain threshold testing. What I thought was interesting here was that they used pressure pain at a number of different potty [ph] sites, so they weren't just targeting specific areas where people had pain. You can see that folks in this first cluster have high pain sensitivity and the worst psychosocial distress. Not surprisingly, those folks had the most pain and the worst disability with their musculoskeletal pain. I added this last night because I felt like we were talking a bit about OPPERA, and somebody had asked about clusters that OPPERA has looked at. Of course, they have an enormous data set, and it probably won't surprise anybody to know those with global symptoms. So they've got all this stuff. Most of the TMD patients fell into this group. Those healthy folks that were in this group were vastly more likely to develop TMD and other pain outcomes. In this particular study, we did...
not find any association between how much pain
increased early on to how much catastrophizing
increases later. We did find a substantial
association between how much catastrophizing
increases early on, and then how that proceeds an
increase in pain.

Coming back to the goal, or what the goal of
my presentation is supposed to be, regardless of
how things started, regardless of what caused what,
it's all present. If we're going to study these
folks, it's all in the soup. If you treat pain,
will the other symptoms improve? We talked about
that a little bit yesterday; if there's a common
shared mechanism, if you treat one thing, will the
rest of these global issues also improve?

I got into this cross-lagged panel thing and
started doing that all over the place. We did that
with a fibromyalgia group that we had. I'll share
you the suspense. This was an exercise clinical
trial, and there was no difference between the
active exercise intervention and the education
control condition. Everybody improved about the
same, which is to say not very much. But we did
find the same association where early decreases in
pain did not proceed decreases later in
catastrophizing, whereas a decrease in
catastrophizing -- now, there was no
catastrophizing intervention, but early decreases
in catastrophizing for whatever reason did proceed
a decrease in pain ratings.

I'm going to talk a little bit about a study
we did with Rob Edwards -- thanks, Rob; these are
all your data -- where we found that the same was
true for total knee replacement. This was an
observational study. We weren't trying to do
anything. There was no clinical trial aspect. We
weren't trying to reduce catastrophizing, but for
whatever reason, there was about a 5-point drop in
catastrophizing on the Pain Catastrophizing Scale,
from pre- to 6-week post-surgery, and that preceded
the decrease in pain that we observed from 6 weeks
to 3-month post.

I want to talk a little bit more about this
project because when I went searching through the
literature for if pain changes, what else changes
to, or if something else changes, does that
decrease pain? I didn't see a lot of papers really
focusing on what those changes are and how they
look over time.

So a little bit about this cohort, mostly
women, 65, overwhelmingly white, and these are the
time points we looked at. Pain just overall
decreased substantially. But as many people here
have mentioned, we had about 25 percent, 30 percent
of people that didn't have all that much pain
relief, and actually 25 percent of people had more
pain at one year than they did at baseline.

What improves when pain improves? Well,
WOMAC definitely improves, and it obscures
everything else. So when you get rid of that, it
looks like pain certainly improves, catastrophizing
decreases substantially, and the sleep variables
that we measured also improved. Nothing really
happened with anxiety, depression, anger, and these
other variables that I would have thought might
have also improved.

Then I started to wonder, well, what about
this 25 percent of people that had more pain a year
out? I would have bet every time that the group
that had more pain a year later had higher baseline
pain, would have worse function, and would have
worse sleep and catastrophizing.

I'm going to spare you the pain of actually
guessing. I would have been wrong every time
because somehow those that had worse pain at a year
actually had less pain at baseline, which makes me
wonder, boy, how do you try to pick these people
out and tease them out early because they don't
have more catastrophizing, they don't have worse
sleep. There's somewhere kind of in that
mid-range, so I was curious about that.

For those that pain actually improves at a
year, which is the overwhelming majority of people,
their pain comes down, obviously. Catastrophizing
comes down. Everything comes down except for
depression. Depression just holds steady. And you
could probably guess for those that had pain that
continued or increased at a year, of course their
pain doesn't improve. There's a spike around
6 weeks in symptoms, but they just come back to
their regular level, and nothing else gets better,
and actually it looks like depression gets a little
worse. I didn't include anxiety and anger on here.
There just stayed flat.

How about if you treat the symptoms? If you
treat pain, we don't have a lot of things that
treat pain super well, unfortunately. So if you
treat the symptoms, will pain improve? We talked
back to catastrophizing, Karen Peterson and some of
her colleagues did this interesting pain coping
skills training with healthy folks, and they did
find that that reduced secondary hyperalgesia to
QST measures.

Now, that was in healthy folks, so take it
how you want. Another group worked on CBT, and
that lowered disability but didn't have long
lasting effects. Then I was really excited a few
years back when Dan Riddle came out with this
experiment. Unfortunately, it was a
quasi-experimental design, so he didn't have an
actual control group, and these were compared to
historical controls. But he found a substantial
reduction in catastrophizing in WOMAC pain
following 18 patients and doing 8 sessions of
pain-coping skills training with them before total
knee replacement.

These are really promising results. I was
very excited. They published a really nice
protocol, but then earlier this year, came out with
their findings, and it was a large multisite
randomized controlled trial. I'm sure you all saw
this, where they had 402 patients; a really nice
sample. These were selected to be high
reduction in catastrophizing in WOMAC pain
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This suggests that we need to do more
research on these areas. It's really important that
we understand the mechanisms behind these
effects, so that we can develop more effective
interventions.

I think we need to consider the
cost-effectiveness of these treatments as well
before we can recommend them widely.

This is a really promising area of research,
and I look forward to seeing more studies in this
direction.
1 to get into those a little bit here. Because if we're talking about doing this on a widespread scale, you can't have a battery of 20 different tests and to think about how to condense those I think would be appropriate.

6 Ezenwa and colleagues, Roger is one of them and I assume was advising them on how to do this. In sickle cell disease patients, they did thermal thresholds on three different areas, two painful, one not painful, and compared those with norms and to the reference site, and bend people into -- they have normal findings, more indicative of central sensitization, which is a good proportion of their folks, or peripheral or a mixed pain group.

16 Tangent on sickle cell disease, we've been talking a lot about fibromyalgia and how that's the poster child for central sensitization. I've been really interested in sickle cell disease. I think it's also a fascinating central sensitization, potentially condition. We knew that, as kids, patients with sickle cell disease don't really have a lot of pain. They have these crises, and there's some black box around the severity, duration, frequency of these crises, and we know by adulthood, somewhere upward of 30 percent have chronic pain. So it seems like an ideal group to try to understand central sensitization and somatosensory amplification.

7 We've been looking at sickle cell disease patients for a while, and we do a whole bunch of QST with them, and it's just a lot. Presenting those kinds of data to the uninitiated feels a little bit overwhelming. It's also overwhelming when you have variables like this, and you want to look at something. So the correlation between QST and X, Y, or Z, well, if you 20 QST variables, that's a whole lot of analyses.

16 You see differences between healthy controls in sickle cell folks on a number of tasks. We set out to try to understand those with central sensitivity or that defined by QST versus those that didn't. So just looking in the sickle cell disease cohort, we created a high CS and a low CS group based on temporal summation, both thermal and mechanical, as well as after sensations. We did not include CPM on this one because our CPM task crashed and burned in these folks.

4 Anyway, 2 of the 4 tasks had to be greater than one standard deviation above the mean of healthy folks. I wanted to delete some of the clutter from the screen so there are no demographic differences other than a body mass index. Not surprisingly, those high in CS were taking lots more short- and long-acting opioids, and you were much more likely to be in that group if you had high CS.

13 We were interested in what differentiates these groups. A high CS person from a low CS sickle cell disease person, they had a lot more pain. They had more crises, more crises related pain, more medical visits. These top data are within 3 months of our initial testing, and if you follow them out -- we followed these people for 18 months, and we found that those in the high CS group had much, much more pain and were more than twice as likely to have -- well, had twice the amount of healthcare utilization as the low CS group.

3 It was also associated with psychosocial factors, so those with high CS also had higher catastrophizing, higher negative affect, lower positive affect, and just a ton of sleep variables. We've talked about sleep. You all are aware there seems to be a really high association between sleep problems and central sensitization.

10 If you Z-score all of these QST variables -- and we're not the first to do that. Roger has shown a lot of these sort of data. So Z-score them to get them all on the same scale, reverse score where needed so that they all face the same direction because for me, it's very confusing if you've got threshold going up and you've got ratings coming down, and making sense of all that. I didn't include the CS variables here, but we did average all of these non-CS, QST variables into one general sensitivity index. You can see that those with high CS had higher general sensitivity.
1 So is there value in being able to show there isn't widespread or peripheral somatosensory amplification? Should we just be getting those CS variables when we're talking about a QST battery? If we're going to recommend that for folks, do they only need to be doing temporal summation and conditioned pain modulation?

2 It turns out they're pretty closely related, more so in chronic pain patients than healthy controls. If you have this continuous measure of central sensitization from those CS QST variables versus general QST sensitivity, you see they are pretty highly correlated.

3 Now, we were really interested in opioids, of course, sickle cell disease. If you split the group into those on chronic long-term opioid therapy versus not, not surprisingly, you see a lot of differences in pain, proportion of days reporting a crisis, and crisis pain. I was wondering if they are just generally sensitive; they're sensitive to everything no matter what we do and what we look at.

4 But that wasn't the case, and I think some of the value in trying to get some of these other QST variables can go to show that kind of difference. The folks on chronic opioid therapy had a higher central sensitivity index, but not general sensitivity. They were pretty much the same on those variables with their non-chronic opioid therapy counterparts. It seems like there's something maybe special about that.

5 I wanted to come back to this quantifying QST a little bit. This is in a different cohort. This is knee osteoarthritis folks, and this is what their QST data looked like. That's a lot of data. We ended up averaging that into those CS variables and those that were QST variables not including the CS. I like that as a way to condense these kind of data and think about them a little bit differently. The other method for doing that, we've talked a little bit. I think Rob showed a Yarnitsky's pain modulation profile and how that could be used. So I went ahead and calculated that in some of our data. Looking at taking temporal summation, if they summate, they get a 1; if they don't summate and stay the same, they get a zero; and if they habituate, they get a negative 1.

6 Doing the same thing with CPM, if it's efficient, they get a negative 1, and you have to reverse it. I was curious to see how those measures stacked up and how they were similar. Again, in Rob's total knee replacement data, we found a higher correlation in central sensitivity index with this pain modulation profile, not surprisingly, that's what we found with general sensitivity.

7 I was curious what mapped on closer to pain in this group, so trying to understand BPI, widespread pain inventory, symptom severity, and it seems like -- well that doesn't seem like. The only variable that was associated with those was this measure of general sensitivity. The central sensitivity did not map on as I might have thought. So it does seem like there's value in trying to understand general sensitivity as opposed to just these temporal summation and CPM variables.

8 I'm not going to get in much to the point about samples. Raj just spoke very nicely on how we might do that. I will say just from a practical sense, it will be a whole lot easier to recruit, make things more generalizable, and probably much more meaningful to include folks that have these overlapping pain conditions instead of just our treatment of choice or our disorder of choice.

9 Now, whether funding bodies, reviewers, and FDA are going to be on board with that, hmmm, but it does seem like stratifying those groups, as Raj was mentioning, makes a whole lot of sense.

10 Should we subgroup or classify participants in any kind of way? We know that QST has been associated with outcomes for a lot of different medications and suggest analgesic benefit. There have been a number of reviews there. I should mention that all of these measures were not specific to central sensitization, so it wasn't just temporal summation and CPM that was used in all of these different trials.

11 Quantifying sensory function might be
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1 interesting. We know that QST has been able to help figure out or differentiate some different treatment effects, so not just analgesic but in multidisciplinary pain treatments, we did some work with spinal cord stimulation that I won’t get into; topical pain treatments.

7 I had the opportunity to work with Jim Campbell -- no relation -- on this clonidine project that he was working on, and it was a really interesting project. He had this clonidine topical formulation. It was a lotion to put on painful diabetic neuropathy patients feet.

13 There was no separation from baseline at the 12-week mark, but he had this idea that if you did a capsaicin challenge prior to giving them the medication -- so putting a smear of capsaicin on the tibia, and just letting that soak in, and getting a pain rating to that -- that those patients might benefit more. Sure enough, those that actually felt pain 3 or higher on capsaicin did improve more with the clonidine treatment.

22 We’ve been talking about a whole lot of variables. There are all these QST variables, psychosocial, behavioral, and physical. I get a little bit confused when we talk about predictors versus outcomes. It feels like they could all be in all bins. We talked a little bit about the BPI yesterday and stole some of my thunder. I was going to mention that we don’t really know what people are rating when we give them a BPI. We use it in our lab.

10 Is it one ring to rule them all? We ask about pain, but we don’t really know if people are giving us pain to the specific knee osteoarthritis that we’re really interested in, if they’re averaging or summing their pain over all of their different body sites, or what’s actually happening there?

17 As we discussed yesterday, it could make people crazy if you try to get them to rate all of their pain to all of the different areas that they mark on one of these maps. It sounds like some people have some good ideas about what can be done there and are trying to consolidate and make things

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1 a little bit easier rate. But as Roger mentioned,
2 you could really get unwieldy with it; ask me about
3 the duration, the frequency of pain, what it looks
4 like, the characteristics. So certainly, coming up
5 with some kind of way to advise people on that I think would be helpful.
6 Focusing on function, I happened to go to
7 this healthy women meeting last week, and one of
8 the things that came out of that meeting, or
9 several people talked about, was how we really need to be focusing on function. Somebody suggested all we need to know is where you are on a scale from thriving to completely bedridden, or somewhere in between. I don’t think it’s quite that simple, but focus on function makes a lot of sense.
10 Turk and colleagues and others from this group have a very nice recent paper on function and how to measure that, the nuances and complexities there. There are functional capacity tasks you can do in the laboratory. There are disease-specific measures you could get. There’s also, I would say, more real-life examples of that, so wearing a pedometer or something like that for some amount of time.
12 Now, if we’re talking about people with somatosensory amplification, and bring it back to that, we probably also need to think about how some percentage of these folks are going to be really sensitive to wearing a Fitbit or an actigraph, and they’re not going to like it.
15 In that fibromyalgia cohort I was describing earlier, a good percentage of those people would not wear a wearable sensor of any kind. Some people took to looping it in some way on their pants, or using a silk strap instead because they didn’t find that as bothersome, but we should be aware, if we’re going to do these trials, that some percent of people are not going to want that, and we should probably think about alternatives to still be able to get real data from those folks.
17 There seems to be this constellation of vulnerability, and we talked about central sensitization and somatosensory amplification, or general sensitivity, whatever we’re going to call
it, on a continuum. I've been wondering if the
distribution of those factors matter, and if
there's any kind of meaningful way to put it
together.
I was wondering if we can take a note from
our cardiovascular colleagues. They've had a lot
of, I don't know, I think success in getting to the
lay public about what the risk factors are for
cardiovascular disease. Maybe I'm just responding
to the nice rainbow-ness of that information, but
I was wondering about the way we present data, and
we typically don't present it, I don't think, in a
very user-friendly fashion.
So I was wondering, well, if we have all
these baseline factors, and we kind of bend them
into some logical things, so clinical pain,
function, laboratory markers, some kind of
sensitivity, and then our space variables, is there
a way to show an additive effect? So this person
has 20 of these issues while this person only has
3, and is there a way to make sense of that?
I was just playing around with this. It
might be completely outside the scope of this
meeting, but it just got me thinking, well, when I
read one of these papers, I usually don't know if
something got a little worse for one pain area or
got a little better for another, or some of those
space variables improved over time.
When I think about trying to see what kind
of recommendations we would make or what kind of
advice I would ask of you all experts, I'd be
curious to know if we are at the point where we
think we can reliably subgroup people and treat
them differently or if we're still at the point of,
well, let's phenotype everything and see what
shakes out later.
It feels like somewhere in between might be
right. What predictors, what outcomes? Is
everything both? Should we recommend using QST?
QST is my bread and butter; that's what we do in
the lab. I'm really interested in it, but I'm sort
of an egghead like that, and I don't know if it
makes sense to really be having our clinical
colleagues trying to do that kind of thing.
especially when we heard yesterday we're not really
at N of 1 anything.
How should we present data if people are
going to do it? Is there a way to reduce that to
make it more meaningful and compelling? Is there a
better way to show what variables are impacted by
others and vice versa? I want to thank all of my
colleagues, collaborators, mentors, and you all for
your attention. Thanks.
(Applause.)
DR. KATZ: Thank you very much, Claudia, for
a very thoughtful and comprehensive presentation.
It is time for a break, so why don't we go
ahead and take that break, and we'll resume
promptly at 10:00.
(Whereupon, at 9:28 a.m., a recess was
taken.)
DR. KATZ: Hello again, everybody. Thanks
so much for being here promptly at 10-ish. Our
next presentation will be given by Dr. Lesley
Arnold, who I've had the pleasure of collaborating
with on a number of different trials in
fibromyalgia and who has been, as you probably all
know, one of the major contributors to clinical
research in fibromyalgia for a number of years now.
That will be our next presentation, then
after that, we'll have time for discussion.
Presentation - Lesley Arnold
DR. ARNOLD: Thank you. It's been a
pleasure to be here, and I've learned a lot from
all of you over the last couple of days. As many
of you know, I spend a lot of my time doing
clinical trials in patients with chronic pain,
especially fibromyalgia, so I'll be mostly speaking
from my experience in working with these patients.
We have made a lot of progress in identifying new
treatments for patients with chronic pain, but I'm
hoping that what we're learning about centralized
pain will advance our studies and open up more
treatment options for our patients.
I thought before I got into dealing with
this problem of comorbidities, I'd thought I'd
share with you a typical day in the clinic with
you, just to give you an idea of what we're talking
My next patient was a single woman. She had depression. She also have high rates of comorbid anxiety and with fibromyalgia, even in primary care settings, surprisingly, since I am psychiatrist, many of my patients are going to have psychiatric comorbidity. Of course, we talked about psychiatric comorbidity yesterday, and of course not surprisingly, since I am psychiatrist, many of my patients are going to have psychiatric comorbidity. But as you saw, in general, population of patients with fibromyalgia, even in primary care settings, also have high rates of comorbid anxiety and depression. My next patient was a single woman. She had a relatively recent history of fibromyalgia, just 4 years, but notice all the medical comorbidities. Number one is obesity, and that's an area that we haven't discussed much. I know Dan mentioned it in his talk somewhat. But it is a very common problem in our chronic pain population, and, yes, it certainly can make pain worse, but there are some more recent information that our fat stores themselves maybe proinflammatory and may be contributing to pain sensitivity. So I think it's an important issue that we need to consider when we are looking at our patients, treating our patients, and designing clinical trials. This patient also had sleep apnea. Again, this is a very common comorbid medical condition. It contributes to sleep disruption, and also as we've heard, sleep disruption contributes to pain sensitivity, so we have to look broadly at many different comorbidities, not just pain comorbidities, when we are designing trials.

This patient also had other pain generators, if you will: osteoarthritis, shoulder impingement, sciatica, hip pain and carpal tunnel syndrome. When we are talking about a fibromyalgia population, and people say, well, can we just focus on fibromyalgia, you're not just going to be able to do that. It's very unusual for a patient not to have other pain disorders. Of course, we talked about psychiatric comorbidity yesterday, and of course not moving on to my next patient, a 3-year history of fibromyalgia, and she also had obesity and spinal problems, degenerative disc disease, osteoarthritis, sciatica, and she also had one of the coexisting overlapping pain conditions that we've been talking about, migraine. One of the interesting aspects of her history is that she has workman's compensation. This is also a major problem that we deal with day to day in our clinic. A substantial minority of our patients do go on disability or have disabling pain, and this becomes a problem for us when we're designing clinical trials, how to deal with that issue and whether being on disability or applying for disability would adversely affect their response to our treatment. So that's something we have to consider when we designed inclusion/exclusion criteria. This patient was relatively healthy otherwise. With regard to her psychiatric comorbidity, she had attention deficit disorder, but we attributed that mostly to having chronic pain, which we know affects cognition.

My next patient, a 36-year-old woman, she had both anxiety and depression. This patient was relatively healthy otherwise. With regard to her psychiatric comorbidity, she had attention deficit disorder, but we attributed that mostly to having chronic pain, which we know affects cognition.
1. It really affects the prognosis long term. It definitely adversely affects it.
2. So that's something else to think about when you're thinking about including a patient in a clinical trial, how do we address that problem? Do we exclude people who have PTSD? Does it affect the prognosis? Yes, it does. So again, something to think about when we're trying to decide what patients to include in a clinical trial.

My next patient is an 18-year-old woman. She had participated in one of our juvenile fibromyalgia studies. She decided to stay with me as a patient, so I've been seeing her for many years. She had migraine as a comorbid pain condition, but she also had very severe psychiatric comorbidity. Her depression led to suicidality and multiple psychiatric hospitalizations, so she has struggled some, mostly, with regard to the comorbidity of depression.

Finally, my last two patients, I had a 74-year-old woman and one of my existing patients. She also struggles with overweight. She has more significant medical comorbidity with regard to diabetes, neuropathic pain, and coronary artery disease. She also has osteoarthritis, so, again, multiple sources of pain and also comorbidity. Depression.

Then finally, another new patient referred by a rheumatologist, a younger woman with just a one-year history of symptoms. She also had problems with obesity and spinal disease, and then she had a couple of the chronic overlapping pain conditions, irritable bowel syndrome and TMD. She had an eating disorder as a psychiatric comorbid condition, which is a little less common in the fibromyalgia population but it does occur. I hope that gives you an idea of what we're dealing with when we're talking about comorbidity and how that can impact our clinical trials.

These are some of the more common chronic overlapping pain conditions that I see in my patients: irritable bowel, chronic headache, interstitial cystitis, temporomandibular disorder, chronic pelvic pain, and low back pain. There are some other ones, but these are the most common that I see.

Again, as we've been talking about, they may be linked by some common pathophysiologic problem, but as we've seen with my patients in the clinic, they have other comorbid conditions that are associated with pain: osteoarthritis, degenerative disc disorder, spinal stenosis, and is very challenging sometimes to figure out what is contributing to their pain experience and how to target our treatments.

Neuropathies are very common in the population, radiculopathies, and we've heard about other rheumatologic disorders. Ehler-Danlos we heard about yesterday. That's a very common problem in my patient population. Then again, the issue with obesity, sleep disorders, especially obstructive sleep apnea, and then depression and anxiety, all of which are associated with pain.

Over the years, we've worked to design clinical trials in fibromyalgia to help advance the field, and we have had success. We have three FDA-approved treatments, but we still need to do more work, and we need to expand access to treatments for all patients with these pain disorders. But there's an effort usually in a clinical trial to reduce heterogeneity if we can, and to try to focus, at least in the fibromyalgia group, on patients who have fibromyalgia as what we think is their primary pain problem.

This is a typical, cut right out of one of our trials, exclusion criteria. It says, "pain due to diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, prior surgery, complex regional syndrome, or other source of pain." By other, it's not really specified, and does not specifically exclude those other chronic overlapping pain conditions. But it's up to the investigator's judgment because it says "in the investigator's opinion, the presence of these other pain conditions would confound or interfere with the assessment of the subject's fibromyalgia pain or require excluded therapies during the participation."
1 So my point being is that it's left to the
2 investigator. Some of this information is not
3 collected by the sponsor of this study, so we don't
4 know, really, how many of our fibromyalgia
5 patients in clinical trials to date have had these
6 conditions. It's not tracked. My guess is that
7 they are in the trials, that most of the patients
8 with fibromyalgia in our clinical trial have
9 multiple other sources of pain, other, if you will,
10 peripheral pain generators.
11 The other exclusion is a little bit more
12 obvious and easier. I think that patients with
13 rheumatoid arthritis, and other kinds of infectious
14 or inflammatory arthritis, or autoimmune diseases,
15 are typically excluded from our fibromyalgia
16 trials, although, again, that excludes an important
17 patient population we have not studied, but at
18 least in these trials, we try to exclude them.
19 But then we can't exclude osteoarthritis; we
20 would have no patients in our trials then. So a
21 way to get around that is to say, well, we'll
22 exclude widespread rheumatic disease. So if they
23 have osteoarthritis in multiple joints, they would
24 be excluded. But again, that's very much left up
25 to the investigator. There are patients who have
26 pretty severe knee OA or low back pain, and they're
27 in these trials. We just don't know the impact of
28 these comorbid pain disorders on our outcomes.
29 As far as psychiatric illness, we heard
30 earlier that the presence of psychiatric
31 comorbidity can adversely affect outcomes and
32 prognosis, so there's an effort to manage that and
33 try to exclude certain comorbid psychiatric
34 illnesses. Psychotic illnesses are always
35 excluded, as is bipolar disorder.
36 We saw yesterday, when we had the review of
37 the comorbid conditions, that bipolar disorder
38 turns out to be more common in the patients with
39 fibromyalgia than in the general population. We
40 don't really know why that is, but patients with
41 bipolar disorder do tend to have more
42 treatment-resistant forms of mood disorder, so it
43 makes sense that they are excluded. But again,
44 that leaves unanswered how would these treatments
45 work in a bipolar population, which is something I
46 see daily in my practice.
47 As far as dealing with depression and
48 anxiety, in the early trials, some of the programs
49 excluded people with current depression as a way to
50 eliminate that problem from the analysis. Other
51 programs allowed depression in and then subgrouped
52 the analysis at the end to see if the presence of
53 depression affected the outcomes or not.
54 More recently, I think what's been
55 acknowledged is that you really can't exclude
56 people who have comorbid current depression
57 anxiety, but you try to manage it by allowing
58 people who have stable, mild levels of depression
59 or anxiety, or if they're on treatment, that that
60 treatment is on a medication that's acceptable
61 during the trial and that the treatment is stable.
62 We typically exclude suicidality for obvious
63 reasons and then also substance-use disorders.
64 We're faced now with a new problem of people taking
65 cannabinoids as these become legal in many states.
66 It's becoming a challenge of how to manage that in
67 a clinical trial. Mostly now it's still excluded,
68 but as we know, people, even if they say they will
69 come off of their cannabinoid for the participation
70 in a trial, it can take several months for that to
71 clear out of the urine drug screen, so it is
72 becoming a problem and a barrier.
73 There are some other exclusion criteria to
74 try to address some these other issues of
75 comorbidity, and the body mass index is one. We
76 have debated with sponsors about where the
77 appropriate cutoff would be for that, and I was
78 saying earlier that in Cincinnati, if you cut it
79 less than 40, I'm not going to get anybody in my
80 trial.
81 We've negotiated somewhere between 40 and 45
82 cutoff, but it is a real problem because the higher
83 the BMI, you introduce more medical comorbidities,
84 perhaps more pain sensitivity, things that we may
85 not totally understand. So we do try to manage
86 that, but again, it gets back to the issue, the
87 more we exclude these people, then we leave out
88 people who might benefit from the treatment. But
When we design these trials, one idea -- and we do that, but I think it's an open question. use the scales. We might have a better effect if how to present these scales and teach them how to develop some consensus around that so that when we affect pain ratings. Maybe there's a way to think we need to do a better job of figuring out how the presence of these comorbid disorders can influence pain scores based upon how patients view this. So I suspect a great deal of variation in the pain severity of these things, have to be treated and stable, so in general, the clinical trial population is going to be healthier and less severely affected. Coming back to then how we view comorbidities when we're looking at our outcome measures, we heard a lot about this earlier today. How are we assessing outcomes, and are we taking all these sources of pain into account when we assess pain severity?

Typically, in a fibromyalgia trial and other chronic pain trials, pain severity is the primary outcome measure. It's typically average pain severity usually measured once daily, in the evening or in the morning, depending on the trial. It's a simple numeric rating scale, 0 to 10, no pain, to 10 being worst pain, or pain as bad as you can imagine.

That's all we're giving patients. In some cases, there is some education provided how to rate that, but in most cases, not. I've had patients come to me during a clinical trial and they'll say, "Well, I know I'm here for fibromyalgia pain, but I wasn't sure. Was I supposed to rate my headache with that? I had this knee pain from my arthritis. Am I supposed to rate that, too, when I'm measuring my pain severity?"

So there's a lot of confusion out there, and I suspect a great deal of variation in the pain scores based upon how patients view this. So I think we need to do a better job of figuring out how the presence of these comorbid disorders can affect pain ratings. Maybe there's a way to develop some consensus around that so that when we have a clinical trial, we're educating the sites on how to present these scales and teach them how to use the scales. We might have a better effect if we do that, but I think it's an open question.

When we design these trials, one idea -- and this is what we're kind of trying to address -- is a centralized pain disorder. You think about fibromyalgia as representing centralized pain that is the end of the continuum, and that these other chronic overlapping pain conditions might be related based upon the presence of this centralization.

I'm quoting Dan here from his slide set earlier yesterday that the phenotype is quite clear: multifocal pain and other CNS symptoms, and in some cases, hypersensitivity to other sensory stimuli. We know that, and that actually is how we define fibromyalgia.

This was an effort to educate primary care clinicians on how to diagnose fibromyalgia and how to simplify it for the clinician. It really emphasizes the chronic widespread pain or chronic multisite pain, however you define it, and then fatigue and sleep disturbance.

In this triad, we were trying to educate our fellow clinicians that If you see this in the clinic, think about fibromyalgia as a possible diagnosis. And of course, these other symptoms are very important to assess, but the idea was to just have them focus in on these three symptoms, and that might improve the recognition of fibromyalgia in the clinic.

Through the work at AAPT, we took that and tried to create a little more simplified diagnostic criteria for fibromyalgia that included multisite pain, moderate or severe sleep problems, or fatigue, and then symptoms present for at least 3 months. This is, again, an effort to try to improve recognition of fibromyalgia in the clinical setting, and we were able to reduce the number of painful sites to 9 possible sites, and then 6 out of these 9 would be a positive result.

This would be fibromyalgia at the end of the continuum, but as we've seen, it may also be useful to look at a more continuous measure. As Dan has proposed and has been doing for other trials, adding a sum measure of fibromyalgia, whether it be syndromal or subsyndromal, might be important in picking out those patients who have centralized...
1 pain, and identify those subset of people who do
2 have -- no matter what pain disorder you're
3 studying, it might be very important, at least
4 maybe in a phase 2 trial, to try to get some
5 proof-of-concept information before going forward
6 with a larger phase 3 trial.
7 In fibromyalgia trials, I think what we can
8 do better is to more specifically identify the
9 other chronic pain disorders that are present in
10 the patient population. For those of you who do
11 clinical trials, you know that we collect medical
12 history in what we call our source documents, and
13 these are like our medical records. Some subset of
14 that information gets transferred to the database,
15 and, really, the sponsor determines what that
16 information will be and what they plan to analyze
17 at the end of the trial.
18 Up until now, they really haven't
19 systematically asked the investigators to identify
20 comorbid pain disorders and to include that on the
21 database. I think just doing that as a first step
22 would be really important for us to at least gather

1 outcome, but, really, is that capturing everything
2 that we want to know about outcomes?
3 We heard yesterday it is important to know
4 how widespread the pain is? Maybe that's an
5 important outcome, or the duration, or are there
6 other aspects of the pain experience that we need
7 to track? Then, do we need to track specifically a
8 regional pain question, abdominal pain with IBS,
9 for example? Do we need to specifically ask a
10 question about that? I would say yes, maybe at
11 least in a phase 2 program where we're just trying
12 to figure out how the drug is working, and then
13 that might inform the larger trial.
14 We've talked a lot about phenotyping. I
15 know this group has dealt a lot with phenotyping,
16 trying to identify subpopulations of patients who
17 might respond to a particular treatment, depending
18 on the mechanism of that treatment. I think that
19 is important to do. Again, we need to track our
20 comorbidity better and maybe utilize some of these
21 QST and imaging maybe in the proof-of-concept
22 trials.

1 some preliminary information about responsiveness
2 of some of these other pain disorders to the
3 treatment.
4 It seems simple to do, but it can get
5 complex because you have to rely on your
6 investigator to diagnose these things, and that is
7 variable across the sites. So we need to give some
8 guidance to them. I know there's some work on
9 trying to simplify that with different screening
10 questions to help the investigators identify
11 whether a patient has IBS, or other disorders, or
12 TMD.
13 Also, even these other conditions like
14 osteoarthritis and neuropathic pain, and other
15 things that we think are getting into the trials,
16 it might be good to know what we really are dealing
17 with, and then we'd have a better idea of what is
18 responding and what is not.
19 Then we have to look at our outcome measures
20 as we've been talking about, and it gets very
21 complex when we think about it. It's been nice in
22 some ways to have a simple one-question primary

The spectroscopy we heard about yesterday
1 has been very effective in identifying how certain
2 drugs might work in patients. So again, at least
3 in the beginning here, trying to incorporate some
4 of these measures in early-stage programs at least
5 would give an idea of how these drugs might work,
6 and what the mechanisms are, and what patients
7 might respond to them.
9 Then even in other chronic pain disorders
10 outside of the fibromyalgia realm, again, assess
11 the degree of centralized pain using one of these
12 scales. It doesn't matter, either including a
13 fibromyalgia diagnostic criteria, a full syndromal
14 fibromyalgia comorbidity, or just a continuous
15 measure looking at the degree of centralized pain a
16 patient may have.
17 That I think would help, again, especially
18 early stage, to figure out what we're dealing with
19 and what patients are then to focus on in the phase
20 3 program. We might get more treatments that would
21 work and beat the placebo in our clinical trial
22 programs.
1 There are a lot of other issues to consider.
2 We've talked about some of these. Catastrophizing
3 has come up a fair amount. In my clinical
4 experience, we looked longitudinally at different
5 factors that predicted outcome and controlled for
6 all of these different factors: medications used;
7 presence of opioids; whether patients were obese or
8 not; whether they use opioids; a lot of factors.
9 The only thing that really predicted a poor
10 prognosis was the presence of catastrophizing at
11 the beginning of the study. But the problem is
12 the patients who entered our study already had
13 pain, so I don't know when the catastrophizing
14 started, if they had it before they developed pain,
15 or if it developed after they developed pain.
16 Nonetheless, it seems to be a sign of a poor
17 prognosis, so maybe we need to identify this in a
18 clinical trial, which we've never really done.
19 We've never looked at this in a medication clinical
20 trial, to my knowledge, one of the big programs for
21 indication. Maybe we need to. Maybe we need to
22 consider that in our inclusion/exclusion criteria.

1 In summary, fibromyalgia is a prototypic
2 centralized pain state. The assessment for the
3 presence of fibromyalgia symptoms, that is
4 centralized pain, may be important in trials of all
5 chronic pain disorders. Identifying these
6 overlapping pain conditions and tracking their
7 response to treatment may be helpful in
8 establishing new therapies.
9 For example, TMD, we really haven't done a
10 lot of medication clinical trials in that
11 condition, and maybe adding some outcomes, again,
12 in an early-stage program, we might get some cues
13 that a new medication might work for these other
14 COPCs; and phenotyping, based on the presence of
15 comorbidity, and using some of these more advanced
16 techniques, might help to identify individuals that
17 are more likely to respond to a particular therapy.
18 Thank you.
19 (Applause.)
20 Q&A and Panel Discussion
21 DR. KATZ: Let me invite all of our speakers
22 from this morning's session to come up and join me

1 There are a lot of other factors that go
2 into designing a trial such as lifestyle factors,
3 stressors, disability, we discussed, and then
4 function. I just want to bring you back to the
5 function piece because we do assess function in our
6 clinical trials, but it's usually one of the
7 secondary outcomes.
8 I think we can do a little bit better with
9 that, maybe. We've worked on developing response
10 indices that include function potentially as a
11 primary outcome. Some of the trials in the past
12 have tried to do that. I think we need to do that
13 a little bit better, and maybe include indices that
14 have functioned as part of it, and then also
15 includes not just pain but maybe sleep, and
16 fatigue, and some of these other very important
17 symptoms so that we really get a good feel of how a
18 drug is working on these multiple domains of
19 fibromyalgia, because we know this condition has a
20 profound impact on people's lives; socioeconomic
21 consequences. We've tried to track these in some
22 of our trials, but I think we can do better.
DR. CLAUW: Yes. This is probably more of a public service announcement than anything else. A couple of years ago, the NIH gave a contract to Bill Maixner and Dave Williams from our group to create a screener for COPCs, and that is almost done. It will be publicly available in the next couple of months. But this will make it a lot easier, in the context of a trial, to screen for all 10 of the chronic overlapping pain conditions in a very short period of time because it asks a couple of leading questions that can say, okay, is it possible the person has irritable bowel? Then it gives the actual criteria for each of the chronic overlapping pain conditions. So it will be the first time in an easy way that people, at the beginning of a trial, could say which of these 10 COPCs someone has. And I do think this would be an incredibly useful thing in phase 2 of an industry trial because you might then see chronic overlapping pain conditions that you have anticipated might be something that you would be going towards with respect to an indication.

DR. KATZ: I think it's worth taking a minute and diving down that rabbit hole one step further since hopefully, we'll come up with actionable recommendations at this meeting. Dan, just made a recommendation, which is that -- I'll try to paraphrase it, Dan -- routinely in chronic pain clinical trials, we should include a screener for these chronic overlapping pain conditions so that we can -- if I can expand on what you said -- better characterize our populations at baseline and even determine whether there's an impact of therapy on these conditions that may or may not be the primary focus of the clinical trial. Is that a reasonable paraphrase?

DR. CLAUW: Perfect.

DR. KATZ: Okay. Who thinks that's a bad idea?
1 put a box around what we're looking at to determine
2 how to define a primary outcome for a disease
3 state?
4 Industry is interested in getting drugs
5 approved. I can't even imagine, based on what
6 we've heard this morning, how that would happen,
7 based on what we've heard this morning. And yet I
8 really believe in central sensitization and I think
9 it's maybe even driving the argument that chronic
10 pain is a separate chronic disease, but we have to
11 define that better. It's possible that Dan's work
12 would allow us to do that, but academic work, not
13 an industry-sponsored trial yet. That's my
14 objection.
15 DR. KATZ: Mike, go ahead. Use the mic,
16 please. Oh, and I forgot to remind everyone to say
17 their name first.
18 DR. ROWBOTHAM: Mike Rowbotham. The
19 screener that is being discussed in the whole
20 presentation yesterday on COPCs is really quite
21 different from what Lesley was saying, which has
22 been my experience recruiting for trials; patients
23 come in, and they've got all sorts of things wrong
24 with them.
25 If you ever want to recruit a patient into
26 your trial, especially fibromyalgia patients, you
27 kind of have to downplay some of those a little
28 bit. And the patients certainly do because they
29 know what the inclusion/exclusion criteria are, and
30 they tailor what they tell you so that they're not
31 going to get kicked out right away.
32 She may want to comment further on that
33 because that's a really tough issue.
34 DR. KATZ: Lesley, you were invited to
35 comment further on that.
36 DR. ARNOLD: Yes, I agree, it's very
37 challenging. I don't think it's just the patients
38 who downplay it. I think some of the
39 investigators -- you know, sometimes we just have
40 to deal with this comorbidity, and we do the best
41 we can. But I was thinking and proposing that
42 maybe we just characterize the patients better and
43 acknowledge that these patients are in our trials,
44 and then find a way to determine, at least at
45 early-stage programs, to see if the presence of
46 these comorbidities affect our outcomes are not.
47 They may not.
48 If these are linked by centralized pain or
49 sensitization, whatever you want to say, maybe they
50 would respond to the same treatments; I don't know.
51 But my proposal is to, well, come out of the closet
52 a little bit about it and just characterize the
53 patients better that we're putting in our trials.
54 DR. KATZ: So still focusing on the issue of
55 whether we should be tracking these comorbidities
56 in clinical trials, I have John and then Clifford,
57 and then Steven.
58 DR. FARRAR: I think there's a push and pull
59 here. There are conflicting components to this
60 that I think Lesley raised very well, which is that
61 you can't exclude everybody. You can't find the
62 one person with only centralized sensitization and
63 nothing else because it doesn't even make sense.
64 On the other hand, there are a group of patients
65 that you do want to exclude, people with
66 significant psychiatric abnormalities.
67 So I think one of the tasks in front of us
68 with regards to this issue of coexisting problems
69 and comorbidities is trying to decide which of that
70 group need to be excluded because they will add so
71 much variability to the measurements that we do,
72 that we can't determine what actually happens
73 versus the ones we include, as Lesley was just
74 saying, and try and deal with as we go through.
75 I was struck by something that was
76 presented -- to, I think Dr. Campbell presented
77 it -- with regards to a study that she was looking
78 at where the depression and anxiety measures did
79 not change, whereas some of the pain measures and
80 other measures did change.
81 I think some of what we are going to need to
82 deal with is to get and look at some of that data
83 to understand whether we can include people with
84 depression, anxiety, or whether we need to measure
85 it. I mean, we certainly need to include them, but
86 the point is how to measure it and how to think
87 about it, and what we decide to do if both of them
88 get better versus one not [sic] getting better and
89
1 one not.
2 So I think the key issue here is trying to
3 dissociate what we can include, stratify, and look
4 at versus the things that we really can't because
5 of the problems that it would impose on the study.
6 DR. KATZ: Clifford?
7 DR. WOOLF: This is a question to the panel,
8 the extent to which the presence of these comorbid
9 features are stable, do they change? When you have
10 your patients -- it looks like a very busy day you
11 had -- when they come back, is the pattern the same
12 for every patient, or for someone who has IBS, does
13 that disappear? In which case, this can make the
14 dynamic nature of that and will add some
15 complexity.
16 DR. ARNOLD: Well, I think, sadly, things
17 stay pretty much the same over time. There is
18 maybe improved coping and living with symptoms, but
19 as part of my clinic, I included the FIQR, the
20 Fibromyalgia Impact Questionnaire, and they fill it
21 out every time they come. It's disheartening
22 sometimes to see how little symptoms change over
23 time. Maybe, again, their coping improves or their
24 adaptation to their symptoms improve. Maybe
25 there's a slight movement of these symptoms. But
26 it's really -- again, my patient population is
27 tertiary care, so you have to keep that in mind.
28 But typically, there's not much movement.
29 DR. KATZ: Although, Of course, if we don't
30 capture it, we don't really -- there could be -- if
31 there was a 40 percent improvement in something, we
32 would probably never know it. It's hard to figure
33 out if people's symptoms are improved without
34 capturing the data.
35 DR. BRUEHL: This is talking about Dan's
36 proposed overlapping pain measure, but I'll frame
37 it as a question. The measure seems to be
38 something that would be very detailed and
39 characterizing diagnostic criteria for a whole
40 variety of potential overlapping pain conditions.
41 But listening across all the presentations so far,
42 it sounds like the reason those are important
43 presumably is because they all reflect some
44 underlying mechanism; and that what we're really
45 focused on is pain.
46 I'm wondering if we're over complexifying by
47 trying to do diagnostic criteria for a whole
48 variety of disorders rather than simply focusing on
49 number of pain sites, which would be a surrogate,
50 because if you've got IC, you've got pain in the
51 pelvis. If you've got migraine, you've got pain in
52 the head.
53 That would show up in a really simple
54 measure. And pragmatically, if you're trying to do
55 trials, would it be easier to say a cutoff out of a
56 number of pain sites at least 4 rather than saying
57 how many in which of the specific conditions you'd
58 have. And I guess I would like comments from the
59 panel as to what they would think of the value of
60 being more simple versus more detailed.
61 DR. KATZ: I think I'm hearing you ask, in
62 addition to a body map, which was a recommendation
63 that floated up yesterday, what additional
64 information is provided that aids in our
65 understanding of these patients by looking at their
66 medical comorbidities, either as a snapshot in time
67 or even past through time?
68 Does anybody have an answer to that question
69 in terms of what additional information is added by
70 the comorbidities? Dan?
71 DR. CLAUW: Yes. So again, I was implying
72 that you would use this in addition to a body map,
73 not instead of a body map.
74 DR. KATZ: Yes.
75 DR. CLAUW: And the reason that I think it's
76 a good idea is that I think that probably half of
77 those chronic overlapping pain conditions don't
78 even currently have a single approved drug. Many
79 of them are visceral pain conditions that are part
80 of trying to get to a chronic pain indication.
81 And I do consult with a lot of people in
82 industry, Lee.
83 DR. SIMON: I know you do.
84 DR. CLAUW: And I think they have often
85 struggled in phase 2 to figure out what conditions
86 their drugs might be effective, and a lot of them
87 are looking and wondering is there a visceral pain
88 condition my centrally acting analgesic might work
in or might work in this or that.

So all I'm saying is that in phase 2, especially if you have a centrally acting compound, putting that in and actually seeing the people that meet criteria for irritable bowel in my study, that there was a strong signal that my drug worked, I think that would be a lot more helpful to the average person in pharma that's trying to convince their leadership that we should take the drug into the great unknown, into vulvodynia, into interstitial cystitis, in these conditions that have not had a lot of drug development and where there is a tremendous unmet need at the level of the patients.

That's all I'm really saying, is that I think it would give a little guidance to say, wow, we saw a really -- if this is a fibromyalgia trial, but we saw that the subset that had irritable bowel, or the subset that had vulvodynia, did really well with this drug, and we actually have data that people met diagnostic criteria for that, and not just had a site on a body map in that location, because that doesn't mean that that person has that chronic overlapping pain condition.

So I'm just suggesting that an understanding of what you're targeting in phase 2 should already have been accomplished, and looking for this kind of stuff, keep it simple. That's the problem.

That also makes an interpretation of the evidence in phase 2 that much more difficult. So search, but don't do it in phase 2.

DR. CLAUW: Then you're developing a new meaning for phase 1 or you're asking for phase 1.5.

And then we're just splitting hairs about -- I'm just saying early in drug development, it would be useful to have this information.

You're conflating I think people that move too rapidly from phase 2 to 3 with me saying that early in phase 2 -- regardless of what we call that, because that's not phase 1. It's not toxicity testing anymore; that early in phase 2 --

DR. KATZ: Let's --

DR. CLAUW: -- 1B or 2A, that's fine. But I'm just saying --

(Crosstalk.)

DR. KATZ: Let's leave that point there.

Mike, you were next.

DR. ROWBOTHAM: I wanted to pick up on something that you said in response to Lesley's comment. One thing that you've proposed is really training research patients, and it's something that we've always tried to do, too; it's very important.

So my cutoff was not so much whether or not they had other conditions -- and conditions that were really outside of what we've been talking about is COPCs -- but whether or not they could actually rate reliably the pain that it is that you're supposed to be testing your treatment for.

I think it's great if you have a really good subject who can rate the disorder that the trial is aimed at, and then independently rate all their other COPCs. Like they can say, "Well, my
musculoskeletal pain got better, but my IBS didn't get better, or my migraines didn't get better. That would be great. I don't think it necessarily has to be at any particular phase because it's going to be a secondary measure anyway.

But the key thing for picking a good subject from a not so good subject, or a subject you really don't want to have in your trials, is whether or not they can be reliable and understand what it is they're rating as opposed to just giving you this kind of global thing of, "Well, I just don't feel good, so therefore even though my FM pain is better, I'm still not happy," or I still don't feel good, and therefore they rate the drug as ineffective.

DR. KATZ: I totally agree with that. Lesley, did you want to add anything to that?

DR. ARNOLD: No, I totally agree with that. As I was giving an example of a patient who came back and asked me what she was supposed to be rating all this time, her headaches or not, clearly, ideally if a patient can differentiate the different pain disorder sources, that would be ideal, but it might be better to, maybe again as secondary outcomes, specifically ask about their IBS pain or their headache pain to separate it out.

I think most people with fibromyalgia understand the widespread achy nature of the fibromyalgia, and they can focus on that, but it can get a little tricky there, too, because I don't know if their low back pain is related, or I don't know if their joint pain is centralized pain, or a mixture of factors. I still think the pain severity is an important primary. I think your programs, and educating patients, and teaching them how to use the scale is good in the beginning and maybe adding some more specific questions about other regional pain disorders might be helpful as secondary or exploratory.

DR. KATZ: In our experience developing these training programs, it's amazing how often when you sit there with a sponsor and try to finalize a program, that reveals lack of clarity about what the sponsor is actually asking the patient and the question in the first place. So putting together these training programs is useful not only for the patients, but also to clarify what it is exactly that we're trying to elicit.

Rick, you were next. Just say your name into the mic, please.

DR. MALAMUT: Hi. Rick Malamut at Collegium Pharma. I have so much to talk about now -- (Laughter.) -- just since I've raised my hand. But I'll start from the beginning, which was John's comment, that totally agree we're going to have to include comorbidities in these studies. It's going to be difficult to find that perfect patient, much less a hundred, much less for phase 3, who meets our predefined criteria of not having too many comorbidities.

I think it's doable to have them in the study. We may want to set limits as to severity. I agree that maybe severe psychiatric conditions -- we have to define that -- may not be the best study patients. Then there are validated scales for some of these; for sleep, for mood, fatigue. It's easy enough to watch those, to attract those, assuming our primary endpoint is a pain outcome. We just have to make sure that our primary endpoint is going to be reliable to make sure the patients can actually reliably tell us that their pain is due to the index condition we're studying.

Then, I have to go back to Lee's comment. I agree with you that some of my colleagues in pharma do try to go too quick, and try to jump from phase 1 to phase 3 without adequate phase 2. Phase 2, as everyone knows in the room, is where studies go to fail. Phase 2 is often thought of as where we learn. So we can use this for registration purposes, but phase 2 is where we learn. So I would suggest that phase 2 for this type of condition is the most important study we run. It's where we look at our population. We look at our outcomes. We see, okay, are these...
viable? We look for those subpopulations. If we have a patient with fibromyalgia who also has TMD, we look to see, did that patient in the subpopulation analysis get better? Do they do worse? And that all helps to guide us with our patient population for phase 3.

I agree dose is important, but it's a little more than that, and we can talk about biomarkers later.

DR. KATZ: Howard, you were next.

DR. FIELDS: The thing that jumped out at me, particularly in Lesley's talk, was how the patients who were rated high in catastrophizing seemed to do poorly in terms of outcome. That raised to me the issue of is that a comorbidity or is that a feature of the primary condition you're trying to treat? If the latter is the case, you might want to exclude them to have a successful trial, but then it might turn out that the drug isn't that effective clinically.

So I'm kind of glad that we have the particular expertise. I was looking over at you, Roger. You seem to raise the possibility that catastrophizing, whatever the neurobiological mechanism is, could actually have a causal role in the condition, or maybe I misunderstood what you said.

DR. FILLINGIM: Well, I think that catastrophizing, along with other psychological factors, could have causal influences on manifestation of the condition and potentially on responses to therapy.

DR. FIELDS: So it's not comorbidity; it's part of the disease being treated.

DR. FILLINGIM: Could be, yes.

DR. FIELDS: Okay. I just raise it because it seems to me to be one of the core problems in clinical trial design.

DR. KATZ: What's the comorbidity versus what's part of the actual disease that we're treating? Yes.

DR. FIELDS: Yes.

DR. KATZ: Roger, did you want to add another comment? You had your hand up.
DR. KATZ: We have not looked at that.

DR. RAJA: Just a quick question related to that. Many of you have done studies in fibromyalgia and chronic overlapping conditions. The question is -- well, a bad patient could be one whose likelihood of dropping out of the study is high because of whatever reason. Do we know if this is a factor in what influences maintaining that patient across the study?

DR. KATZ: The retention rates in the fibromyalgia studies have been pretty good, I think. No?

DR. RAJA: But have they excluded those high catastrophizers?

DR. KATZ: Oh, I see; catastrophizing per se rather than -- it doesn't seem like widespread pain itself is a reason for people dropping out because the fibromyalgia patients, they don't seem to drop out for much. But in terms of catastrophizing per se, I don't know the answer. Does anybody know whether catastrophizing is a predictor of a dropout?

DR. WASAN: There's no data on that.

DR. KATZ: Okay.

DR. WASAN: Just as far as I can -- Rob, do you agree? I haven't seen a single thing.

DR. EDWARDS: Along those lines I think it has emerged from the placebo literature that the expectation of a negative outcome has a big influence on actually the outcome being negative. One might expect that a catastrophizer would be pessimistic about the outcome. There was a recent article, actually, from Fabrizio Benedetti I was talking about with someone yesterday, where they were looking at injections for set joint pain, either lidocaine or saline. Saline was the placebo. People that thought they got the active drug, even if they had the placebo, were the ones that did well. There was a bigger effect of expectation than there was of the local injection. So it seems like it's a conundrum. If catastrophizing is really a feature of the disease and has a negative influence on the outcome of your treatment, you've got to figure out a way to deal with that particular problem. One possibility is just asking people whether they think they got the active treatment. If you think they got it or they think they didn't, you might group those together and look at the difference with the medication. That's what they did in that study that turned out to be very useful, so that's something to think about in terms of an analysis of the outcome. If you don't do that, then you're going to introduce a lot of variability based on people's expectations.

DR. KATZ: Right. Luana?

DR. COLLOCA: It's interesting that we don't have too many papers exploring the relationship between catastrophizing and expectancy, but this is a great point because it is not so demanding in terms of cost, and any clinical trial can be complemented with this measurement that can be extremely important to help us in interpreting data, but maybe also stratifying the patient when we run clinical trials.

DR. KATZ: I have to say that I see pharmaceutical companies increasingly incorporating measures of masking, if you will, or expectation in their clinical trials often because they expect -- no pun intended -- that they're going to be asked to evaluate whether side effects, for example, caused on masking, which in turn was responsible for the treatment benefit that was observed. So they need to have that data on hand in order to address that question. I wouldn't say it's universally done, far from it, but I see it increasingly done.

Ian and then Ajay.

DR. GILRON: Should I move on?

DR. KATZ: Okay. Let me actually summarize where we are with this topic on measuring comorbidities, and then we can move on to if there any other clarifying questions about the presentations. It sounds like there's a general support for the idea of measuring not only a body map, but also...
1. There's some additional information that can be gained by measuring comorbidities. We have Dan's tool that will come out eventually. It could be used for that purpose.

2. A number of people mentioned and a number of important potential unintended consequences of that or a caveats, such as how that's going to impact our inclusion/exclusion criteria for these trials once you started revealing that these patients in fact do have comorbidities that we might have been happier to sweep under the rug before, and some other caveats as well. And those caveats need to be considered as well in making that decision.

3. That's what I got out of that whole conversation. I think we can move on to other questions or comments about the presentations.

4. **DR. GILRON:** Ian Gilron from Queen's in Canada. First of all, thanks to everyone for amazing talks this morning. My question relates to Raj's what's in a name and how it leads to identifying participants for a proposed trial.

5. This is not a rant, but let me just unpack it a little bit. It seems to me that the important distinctions here, dealing with central sensitization or whatever we might call it, are do we have sensitization or is the sensory nervous system normal? Is it central versus peripheral sensitization? Is that important? And is there a known source of nociception versus no identifiable source of nociception?

6. I'm thinking back to what was done in neuropathic pain. For example, in 2008, Rolf-Detlef Treede and Charles Jensen and others were working on a grading system for diagnosing neuropathic pain, using an approach with history, physical, and as needed, special investigations to come up with a designation of probable neuropathic pain likely or -- sorry, definite, probable, or likely neuropathic pain, and I wonder if we need that here.

7. So my question is must we, or should we, include an objective or at least clinician observed measure to confirm sensitization of the nervous system, for example, such as QST patterns compared to population norms as an inclusion criterion for central sensitization?

8. **DR. KATZ:** So let's break that down a little bit because, Ian, I think you brought up two kind of companion issues. The first one is, which I think is the big pink elephant in the room, is central sensitization one thing or is it multiple things? And if it's multiple things, what are those multiple things?

9. That's issue number one, and then a separate issue would be, what is the best way to measure it, or to diagnose it, or what-have-you? I think it might be easier to put the measurement issues aside and just deal with the conceptual categorization first, which is the first thing you brought up; is central sensitization one thing or multiple things?

10. And if so, if it's a multiple, what are those multiple things?

11. We can debate about names but at least maybe agree on the concepts first. And you actually proposed a classification system, if I was listening to you correctly, where you proposed that we could classify these patients based on whether there is or is not an identifiable source of nociception, and whether there is or is not sensitization. And if there is sensitization, is it peripheral or central? That's what I heard you say as an initial kind of draft classification system, if you will.

12. Maybe start with the speakers first. Maybe start with you, Raj, first. You were specifically called out. Is central sensitization one thing or multiple things? And if it's multiple, what are the subtypes?

13. **DR. RAJA:** I think going back to the issue of do we need something along the lines of what the neuropathic group did, I would say, yes, that might be helpful. Again, going back to the analogy of -- and Steve can add to this -- complex regional pain syndrome, we had a whole cluster of names, a whole cluster of symptom complexes. Until they came up with some kind of clear clusters of symptoms, and then signs, and the presence of them...
or not, I think the field was lagging behind because each specialty was calling this differently, and the studies were done differently. So I think to be able to advance this field, we have to come with kind of a paradigm of sorts, and this paradigm could be initially based on history, based on some exam factors and some biomarkers, whatever it would be. But I think coming up with a protocol and saying these are the likely patients to have central sensitization, or these are definitely the patients, I don't think is going to help advance this field.

DR. KATZ: So you're advocating an effort to try to create more clarity around the typology of central sensitization.

DR. FIELDS: I'm going to vote for multiple.

DR. KATZ: You're going to vote for multiple? What are they? What are the multiple types?

DR. FIELDS: Well, they're in Clifford Woolf's review article. You can have a loss gabaergic inefficient. You can have excitation. You can have amplification by descending facilitation. So there are a variety of mechanisms centrally that could give rise to what we observe clinically. DR. RAJA: That could be the subtypes within a broad group.

DR. KATZ: So let's talk about the subtypes of what we observe clinically. What are those subtypes?

DR. RAJA: Could you get Steve's comment on what he thinks based on what's happened in that --

DR. BRUEHL: I was just going to say, I totally understand Howard's desire to break things out by mechanisms, and I also appreciate Roger's comment about lack of clarity, like disagreement on what the basic concepts are. And there's a big parallel with CRPS, many names, many presumed mechanisms.

I sat in on several expert meetings where the people that knew the most about the mechanisms of CRPS all felt like it was important to have a mechanism-based diagnosis but were basically saying we don't know enough about the details of the mechanisms to convincingly argue that we should diagnose based on that. As a result, what happened was it was more of an umbrella term first, which was designed to get everybody using the same terminology and the same criteria, although, granted, they are probably over inclusive. And then we shrunk it down a little bit with revised criteria, and probably will do that further considering subtypes now that may indeed be mechanism based.

I think in the context of talking about what we're talking about here, there are a lot of parallels. We don't agree on terminology, so I think having that would be valuable so at least everybody's on the same page. When I look at the mechanisms or the indicators of mechanisms we've talked about, what I kind of see are three distinct buckets, and I will throw this out for comment. One seems to be central sensitization as originally defined, where Clifford was talking about you've got a stimulus and response and you've got a hyper responsivness that you see, and maybe QST is the way to best assess that. But that's one bucket that would be that pure traditional central sensitization.

Then separately, we've got a number of body sites, maybe chronic overlapping pain conditions based on diagnostic criteria, and according to Dan's cluster analysis, the general sensitivity issue. All those things seem to hang together. Then separately we have the negative affect catastrophizing issue, which seems to be important and may be related to central sensitivity, but is kind of not really the same thing as the other two. All of these, of course, may interrelate. I wonder about the best starting places here; whether you start with a broad label, you collect data on all of these buckets, and then get a sufficient number of patients to be able to empirically decide what mechanisms might be supported, or if you go the other way around and say, a priori, we're going to say we think these mechanisms are involved, and that's kind of what we do eventually to come up.
with what the proper label is.
2 Sorry for the length of that.
3 DR. KATZ: For the moment, would people
4 agree that central sensitization and the presence
5 of some kind of peripheral injury, a nerve injury
6 or osteoarthritis of the knee or what-have-you, is
7 a different subtype than people with, let's say,
8 pure fibromyalgia, where they have widespread pain
9 and hypersensitivity without any obvious peripheral
10 injury?
11 Would people agree that those are -- at
12 least how separable they are in terms of the
13 realities of measurements is another thing, but are
14 they conceptually different? Yes; so that's two
15 subtypes.
16 I had Ian, and then Mike.
17 DR. GILRON: I'm just wondering -- just
18 coming back to Howard's comment of parsing this
19 out, and maybe Clifford can help -- for example, if
20 someone has loss of descending inhibition as a
21 predominant mechanism for their widespread pain, is
22 that actually central sensitization per se or is it
23 just impaired inhibition?
24 DR. KATZ: Clifford?
25 DR. GILRON: I don't know if that semantic
26 is important.
27 DR. WOOLF: To take a slightly different
28 take of this, it seems to me we want to try and
29 capture enough information so that we can identify
30 who responds to different treatment modalities.
31 Again, unfortunately, that's a chicken and egg.
32 Once we have different treatment modalities that do
33 act on different aspects of this phenomenon, that
34 may help us identify the differences that exist in
35 outpatients.
36 We don't know enough, I think it's fair to
37 say, at the moment, mechanistically, about the
38 underpinnings of these different forms of
39 centralized pain to be able to say which one is
40 disinhibition, which one is facilitation, which one
41 is predominantly spinal cord, and which one is in
42 the higher brain centers. But if we see patterns
43 of differential responsiveness to this treatment
44 versus that, that may actually help inform us in a
45 way.
46 I would add that definitely to the mix as
47 part of the way in which we classify who responds
48 to what or what kinds of patients respond with
49 which particular therapist and what aspects of
50 their pain or response? Is it only the tactile
51 alldynia or is it some other aspect of pain?
52 DR. KATZ: So are you saying that you think
53 that loss of inhibition is a salient enough
54 phenomenon that contributes to these clinical
55 features that it's worth characterizing if we're
56 doing a study, and we're attempting to understand
57 the impact of a treatment on central sensitization?
58 DR. WOOLF: What I'm saying is I don't think
59 we know enough now in terms of being able to
60 identify an individual patient if they have
61 disinhibition versus any other mechanisms.
62 DR. KATZ: I see.
63 DR. WOOLF: But as part of our attempt to do
64 that, whether functional imaging or other
65 techniques may enable us to identify what is the
66 predominant mechanism, I think that part of that
67 may be treatment response. So it's not just using
68 this to identify treatment response, but it's
69 actually that treatment response itself may help
70 give us mechanistic insight.
71 DR. KATZ: Right. Actually, Ajay, you had
72 your hand up earlier, and I lost track of you, and
73 then I have Simon. Who else wants else wants to
74 get in the queue? Mike and Jim; everybody wants to
75 talk. Go ahead.
76 (Laughter.)
77 DR. KATZ: I'll just go by the rows.
78 DR. WASAN: First of all, I'm Ajay Wasan.
79 Secondly is that I agree with Steve and even some
80 of the comments from Clifford and others, that it's
81 just too much to say we should be able to classify
82 it by mechanism. But I think we can propose a
83 framework that is an advance that allows,
84 subsequently, to fill in some of these mechanisms.
85 For instance, I think that this concept that
86 there is somatosensory amplification, a feature of
87 many chronic pain syndromes, that they're
88 independent contributions of brain, of spinal cord,
1 and peripheral nerves, and also the interactions of
2 those is important. And of course, not all of
3 those potential mechanisms are operative in every
4 single patient and in every single condition.
5 But we can provide that simple framework,
6 that there's -- even now, just articulating that
7 there's independent contributions of the brain to
8 creating facilitation, for instance, of
9 amplification is in itself an advance. I mean, it
10 really is a significant step forward.
11 So I think proposing that type of framework
12 is really an advance that this group can, with the
13 context of, but we don't know, of course, all those
14 mechanisms, and what they are, and how to classify
15 them, and how do they want individual patient, and
16 how to assess. That's where I think the framework
17 idea may hold some water.
18 DR. KATZ: Thanks. You get speaker's
19 privilege, Lesley.
20 DR. ARNOLD: Well, thanks. I guess I
21 question the idea of this pure fibromyalgia
22 top-down only because I don't think we know enough

1 someone who is in chronic pain, they're already
2 using their, whatever, descending inhibitory
3 control they have, and this additional conditioning
4 stimulus will apply second conditioning pain.
5 So it might be that we're not able to at
6 least get extra response to sort of second
7 conditioning stimulus rather than we'll label them
8 as someone who's descending inhibition doesn't
9 work. So I think we need to be somewhat careful
10 and not label patients with inability to facilitate
11 descending inhibitory control in a sense. So it
12 depends on the testing paradigm, we should be just
13 careful.
14 DR. KATZ: Thanks. Mike, you were next.
15 DR. ROWBOTHAM: I think you'd have a hard
time finding a fibromyalgia patient who when they
17 tell you their story doesn't have some sort of
18 inciting event, injury, flu-like illness, sports
19 injury, something that they kind of tied onset of
20 their symptoms to.
21 One thing I wanted to get back to, and I
22 thought about it just by Vitaly's talk yesterday,

1 about peripheral inputs to be able to say that the
2 peripheral input is not also important. I
3 mentioned obesity as an example. It's not an
4 injury, but it's a metabolic change, and that can
5 affect how the brain is functioning.
6 So I just want to be careful not to separate
7 it like that. I think this framework that Ajay
8 presented is I think a good way to look at it, that
9 there are these multiple possible mechanisms. We
10 don't always know what's operating in an individual
11 patient, but to present this as these are the
12 possible parts to the puzzle is important. I'm
13 very cautious right now of dividing the group just
14 yet until we have more data.
15 DR. KATZ: Thank you. Simon?
16 DR. HAROUTOUNIAN: I just wanted to caution
17 ourselves against labeling people as patients who
18 have loss of descending inhibition because I think
19 it really depends on the testing paradigm. When we
20 test descending inhibition in healthy volunteers,
21 we apply some sort of conditioning stimulus, and
22 then look at the response to test stimulus. But

1 is there is sensitization, I believe in that, but
2 that's perhaps on top of an underlying tendency
3 that's really a personality trait towards this
4 somatosensory amplification. That would fit with a
5 lot of the genetic data in patients with migraine,
6 where there's heritability and other kinds of
7 things; that you're not really going to be able to
8 medicate that part away. You may be able to
9 medicate away the overlying sensitization, but
10 you're not going to change personality.
11 So the data that Vitaly was showing
12 yesterday that was really compelling was where you
13 looked at the brain activation, and it was the
14 same, but it was the same based on the percept
15 rather than the same based on the stimulus
16 intensity. I think that's really very important.
17 Unfortunately, the OPPERA study came close
18 to getting some of that kind of data, but I don't
19 think it really went -- and I'd like to be
20 corrected if I'm not right on this. But it doesn't
21 necessarily go back far enough to get at what the
22 patients were like long before they developed TMD
1 or any of these other COPC grouping of conditions.

DR. KATZ: Thanks. I have Jim Rathmell next.

DR. RATHMELL: I think it's mostly been said, but I want to restate, let's be pragmatic about how at the bedside you're going to be able to characterize some of these things. There are these tests that can sort out the inhibition versus amplification, and are we really going to insert those into the clinical trials as the paradigm for selecting people, or is it just going to be additional information?

I think we're getting to a point where I'm getting foggy on how you would actually select the patient for characterization. But one of the things that Clifford just said is interesting, is you could say based on their initial response to therapy, X, Y, or Z during an enrichment period, you could label them mechanistically because of the response to an individual drug and say we think this is the mechanism, and then carry forward from there; so if you're trying to select based on their response, or you may even screen them with a panel of different drugs to select the ones that respond to drug X, Y, or Z because of the mechanism that underlies that. That would be an interesting paradigm.

DR. KATZ: Dan, you actually were next in the queue.

DR. CLAUW: If I could just respond to a couple of things. One, first of all, there's absolutely no evidence that this is a personality disorder, so I'm just going to push back very strongly on that, but that's not the main point that I want to make.

The main point that I want to make is I just want to agree with the fact that even though our group does a lot of imaging, QST, and things like that, we've published a lot of studies where we take individuals with fibromyalgia, we do QST and imaging, we give them a treatment, and we then go back and see what predicted what worked. In many cases, we are at an a priori hypotheses about the imaging findings that would predict responsiveness, and we were right, but we have never been able to go back afterwards and say, okay, now we see this group of responders; let's go back and look at their clinical symptoms. It would have been easily collected at the point of care or in a trial, and tried to say which subset. That was the same with all the fibromyalgia studies, registration trials that were done with pregabalin and duloxetine. Even though we intuitively thought the people with more depression would respond to duloxetine, and the people with more sleep problems would respond to pregabalin. It was very difficult, actually, to ever see that you could, a priori, based on the predominant symptom or anything, predict who was going to respond to the treatment.

So I'm just saying that even though I love these mechanistic studies, I don't think any of them are ready to be embedded into clinical trials because, again, the clinical trials, at least for the foreseeable future, are going to be looking at PROs or things like that, or QST. But again, QST doesn't do it. It's not strong enough.

DR. KATZ: I have Ian, and then John Farrar, and then Sharon Hertz.

DR. GILRON: Just coming back to a diagnostic test or a diagnostic process for this, I'm hearing comments that this is a little bit contrived, and to hang our hat on something like that would be difficult given our understanding the complexity of that.

Within this room, I think we can all appreciate that and would probably have some consensus on knowing who we're looking for when we see them, that this looks like who we're talking about, but coming up with a definition, particularly if we get to, at some point down the road, labeling indication -- to get to the point of how we're going to define our inclusion criteria. I feel like we have the need to at least come up with some sort of clinician observed measure that is more than just history or self-report measures.

DR. KATZ: John?
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<td><strong>DR. FARRAR:</strong> I'm struck by the problem that we're trying to address and the lack of specificity, if you like, on what it is that we're actually talking about. I'm a strong believer in the centralization process. As Clifford has suggested, and Howard, there might be multiple mechanisms that underlie that. I'm also very much struck by the fact that the cause may not be the same process that maintains that. My analogy is once the car has wrapped itself around the tree, fixing or doing something with the brakes isn't going to help very much. I guess what I'm struggling with is trying, as Ian is saying, about how do we identify the group. What strikes me is that a couple of people now have said that there is a peripherally maintained chronic pain centralization or chronic pain enhancement; the example given of injecting into the nerve endings of people who've lost limbs, and finding that a lot of their phantom pain can go away. My guess is there are two groups. There are the people in which you can do that, and it goes away, and there are people you can try it on, and it doesn't go away, and that might be a proactive way of actually defining certain groups. Now, I don't know how to do that, but it seems to me that if we could come up with some mechanisms for actually trying to characterize the pain -- Mike's work in postherpetic neuralgia, the capsaicin sensitive versus the capsaicin insensitive, I'm not sure what they are, but it seems to me that at least some thought about ways to not simply measure and gather patient-reported outcomes, but to do some sort of testing to understand -- we had the imaging data yesterday, where given a pressure of 4 on the finger, some people had a much bigger response than others. So I would just raise that as a question for the group in terms of whether there are ways to think about categorizing our underlying mechanisms in a way that would allow us to better address them.</td>
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| **DR. KATZ:** Sharon Hertz? **DR. HERTZ:** I keep hearing about QST, and I'm wondering if there is a thing that everybody is referring to that is the same. And if not, what is the range of what's going on out there and how does that impact understanding the results? **DR. KATZ:** Would anybody like to answer Sharon's question about what are people doing out there that they call QST and what's the variability in terms of what's actually done? **DR. FARRAR:** Maybe Dr. Campbell. It's your lot. **DR. ARNOLD:** I could try. I think there's enormous variability in QST responses. There are a lot of different tasks that people do. We include a battery that covers a lot of different domains and takes about an hour. We could never expect a clinician or somebody that's trying to quantify the person right in front of them to do anything like that; nor do we have normative data. The German Research Network has tried to do some of that work. I imagine between some of us here in this room, we could probably come out with norms, but I still think even if we did that, it would probably be unreasonable to expect somebody to do any kind of deep phenotyping at the outset of a trial. So I think that's tricky. There's huge variability that I think can obscure what you're trying to look at. Like Dan was saying with some of these psychosocial and behavioral factors, we can look later on at the end of the trial and see if we can predict outcome based on baseline responses to X, Y, Z QST measure. I don't think we've done as good a job about testing those various factors over time, and I actually had the same complaint over some of our psychosocial, behavioral, and widespread pain questions. I think we do a fairly decent job getting some of these measures at baseline, but then don't necessarily follow them and look at trends over time to be able to identify who did better and what outcomes that improved. **DR. HERTZ:** Just to follow up, there's a lot to choose from. I'm assuming there are different
systems to run them on. And then we have to wonder about inter-rater or performer reliability. It sounds like -- when I hear conclusions based on QST, I'm not entirely sure what it means. It's like saying, well, we evaluated the patient, and there was no correlate with the evaluation. It's just this box of something that goes into it. So I'm just wondering if moving forward, there's any interest, or stomach, or ability to consider defining some parameters so that when we look study to study or population to population, we have some idea of what this QST means. Because when we're trying to think of what might actually be useful and pragmatic in a clinical trial setting, when it comes to this kind of thing, QST in particular and no matter what it's being directed at, everyone and their brother wants to use it because they think it will somehow get them something. And with a lack of any consensus on the kinds of parameters, the type of testing, and comparing different operating equipment, how are we going to really understand the findings from one study to one study, or from one program to another?

DR. KATZ: Steven?

DR. BRUEHL: Just to address some of those issues, I do get the sense, there is a lot of variety in ways you can do QST, but I think the most commonly used method is the computerized heat pain, which seems to be pretty consistent across a lot of locations, often using exactly the same equipment, at least by the same company. So I think there is some consistency in that. CPM, we call it CPM, but it is a whole bunch of different procedures, and I don't think there's any consistency on that at all because there are so many permutations of stimuli you can use in that. And I know that there is some work done that show you get very different results, depending on the particular combination of stimuli, whether it's heat and cold, or heat and pressure, or whatever it may be.

For APS a few years ago, I was asked to review reliability information on these commonly used QST measures, which nobody really talks about. And at that time, it was very clear that tolerance and threshold are both pretty reliable and have good reliability. Temporal summation is not quite as high, but it's still reasonably reliable, and CPM was not very good at all. It made me wonder whether CPM is a state rather than a trait, whereas maybe temporal summation is more something trait-wise that we're assessing.

I just thought I would throw that out. There is a lot of inconsistency, but they can be reliable measures. And in terms of Jim's comment about pragmatic, the temporal summation option using von Frey hairs is very simple to do in a bedside setting. So that would be very pragmatic. It has been used in several studies, although it doesn't seem like everybody uses the same pressure, and I'm not sure what the data are on reliability of that.

DR. KATZ: We've actually published data on the reliability of temporal summation using von Frey filaments in osteoarthritis, which showed that it was pretty reliable. And in that same paper, we published data on the reliability of CPM, showing that it was not that reliable, so there is some data out there.

Yes, Joachim?

DR. SCHOLZ: I have a comment regarding the specificity of these assessments. It seems like the reference could be maybe healthy population, but I don't think that would be adequate because then the outcome would more refer to we define central sensitization as increased pain sensitivity, and that cannot be the objective. It is defined as a particular mechanism. So our reference should rather be a group of patients who have a painful condition but do not display signs that we consider specific for central sensitization. I think that's where it becomes a little bit tricky, so we would have to think also about methods to rule peripheral sensitization or have a clear understanding of the concept of how
central sensitization can look clinically. I don’t think that’s precisely defined yet.

DR. SCHOLZ: Okay. I don’t think we have a clear understanding of the clinical concept, how can central sensitization look in a patient other than just increased sensitivity. I’m not quite convinced that I have heard that during our discussion.

DR. KATZ: Sharon, did those comments address your question?

DR. HERTZ: Somewhat, yes.

DR. KATZ: Sharon, did those comments address your question?

DR. HERTZ: Somewhat, yes.

DR. KATZ: I think the answer is you’re right. There are a lot of things going on there with no clear standards. And you’re suggesting that it would be useful to have such standards, and I think the group heard your suggestion.

DR. CAMPBELL: Just to add one thing. Going off of what Steve mentioned, those static tests, so threshold, tolerance, do seem to be more stable and trait like, but I think Yarnitsky and some other folks have suggested that these tests that are potentially more central sensitivity related, like temporal summation and conditioned pain modulation, might be more malleable and potentially more responsive to treatment, and might be -- I don’t want to say better -- different measures you could use to potentially get at some of that.

DR. KATZ: Sharon, would it help you folks to have some kind of a review handy that outlined what the techniques are that have been -- like Steve’s review, what are the specific techniques, how exactly are they done, and what is the reliability of the specific technique as it's done? Would that be useful information for you?

DR. HERTZ: No -- (Laughter.)

DR. HERTZ: -- because --

DR. KATZ: Then I won’t bother.

DR. HERTZ: -- I mean, yes and no. What’s useful is what's going to be actually done out there. I don’t want to direct a large project to occur if it's not going to be consistent with anybody's approach -- I don't want to create work that's not going to be then utilized -- I mean, it will be interesting. I'd like to read it, but I don’t know if that's the reason to do all that work.

DR. KATZ: Mike?

DR. ROWBOTHAM: I just wanted to comment to Dan that I was not implying this is a personality disorder. I was talking about personality traits; so not personality disorder as in what used to be called the somatoform disorders or somatization disorder and now are called, in DSM-5, somatic symptom disorder. I'm just talking about enduring underlying personality traits that are likely to remain pretty constant over many years.

DR. KATZ: Clifford?

DR. WOOLF: To address Sharon’s question about the utility of QST, at least I think I remember correctly, there’s a paper by Ralf Baron and Roy Freeman, claiming that patients with tactile allodynia were the ones who responded to pregabalin, and those who didn't did not. To me, that is where you could get value from these kinds of measurements. It helps identify responders.

DR. KATZ: And those were done with simple bedside techniques in that particular study, yes.

Simon?

DR. HAROUTOUNIAN: We just did the same thing prospectively in trying to see patients with baseline mechanical sensitivity [indiscernible] to respond to pregabalin, and they didn’t. We just published it in Pain.

(Laughter.)

DR. KATZ: Dan?

DR. CLAUW: I want to give another anti-QST. Steve Hart in our group leads the QST for three big NIH networks, the MAPP and two other big networks studies, a thousand people in the MAPP and hundreds in the other networks. All the things that people have said are true. There are issues of reliability and norms and things like that, but that's not what bothers me about QST.

What bothers me is that the predictive power
of it in any of those studies is weak. Our values are 0.3, 0.4. You can get statistical significance, but they don't come close to the point that you would use them to make clinical decisions or things like, and that's where I have probably a bigger problem with QST. I think you can actually circumvent some of the problems of standardization across sites, dealing with inter-rater reliability and normative data. It's just that it simply doesn't -- compared to the patient-reported outcomes or the imaging, where we have all of those in all of our studies, over and over and over again, the QST is not strongly telling us anything.

That's the cautionary note, and I agree with Sharon. It's like part of it is like the validity, and I'd be interested in it, and we still do it to try to infer mechanisms, but I'm just giving this cautionary note that I just don't think it tells you that much that you can't glean with simpler measures.

Specifically on that, as I'm also involved in the MAPP program and know about Steve's work, I agree with you that it has not worked well in those situations, but getting to Sharon's perspective, all of MAPP-1, the QST consisted of thumb pressure. It was a single measure. There was no temporal summation studies. So I'm not disagreeing that it has not worked in the studies that Steve has been involved in. My thought would be that perhaps we just don't understand what we're doing there very well, and that if we're looking for temporal summation as an indication of centralization, then we should do temporal summation, and we should look to see if that's predictive, and I'm not sure that that's been done.

Look at OPPERA.

Could you speak into your mic, Dan? OPPERA did 10 QST measures, and none of them have an odds ratio greater than 2 in predicting anything.

DR. FILLINGIM: Well, we've sort of been going back and forth on getting more specific in identifying mechanisms for whatever this thing is we're talking about, or these things, versus looking at a global phenotype or subphenotypes. And those are all different initiatives. I think it relates to this conversation about QST. So if I want to predict mortality, I can ask people about specific conditions they have, or I could ask them, overall, how healthy do you feel. And how healthy they feel is going to be a better predictor of mortality, I suspect, than really specific questions about their health.

I think we get into the same phenomenon with patient-reported outcomes, which they can subsume a lot of constructs, and each construct may actually have additive predictive value. So that global construct is predictive, but it doesn't tell us much about mechanisms to the extent we might be interested. Then if we drill down into subphenotypes or methods like QST that we think are a bit closer to mechanisms, we sort of keep drilling down, and I suspect we're going to have to find some happy medium somewhere in there. But I think that's some of the tension here.

DR. KATZ: We have a few minutes left to go in this morning's discussion. Does anybody feel prepared to articulate a proposal for how we're going to identify this group of patients with central sensitization, whether it's one thing or more than one thing and how to identify them just as an appetizer for the afternoon's discussion?

DR. BRUEHL: I just want to ask a question, which is if we look at the title of this conference, we're talking about central sensitization, somatosensory amplification kind of as a bundled thing, but we've spent a lot of time talking about chronic overlapping pain conditions. I guess what I wonder is, is that something separate from central sensitization or is that one of the components we're considering to be part of that?
DR. KATZ: Anyone on the panel want to answer that?

DR. FILLINGIM: So the answer is yes. (Laughter.)

DR. KATZ: Yes what? (Laughter.)

DR. KATZ: Can you expand on that one-word answer a little bit, Roger?

(DR. FILLINGIM: No response.)

DR. KATZ: Sorry. No answer. Personally, I think that -- actually, Dan, why don't you answer that question? Chronic overlapping pain conditions, are they part of the definition of central sensitization or are they just patient characteristics that we want to track as we're performing clinical trials? What is its role on a conversation about central sensitization?

DR. CLAUW: If I had to define them, I would say that these are clinical conditions that overlap a great deal with each other, both in individuals and families, and seem to have shared mechanisms and prominent central nervous system mechanisms. I think central sensitization is playing a role in all of the chronic overlapping pain conditions, but I think it also plays a role in any chronic pain state. There's a subset of people with any chronic pain condition that have central sensitization. So I think the only thing that really sets the COPCs apart from any number of other pain conditions is that maybe the central factors are more front and center in those conditions. But again, you take any of the COPCs, and you can identify, again, 20 percent of people with interstitial cystitis that clearly have just a bladder problem; that they don't have anything that would look like central sensitization. You can identify 15 percent of people with temporomandibular disorder that clearly have a TMJ joint problem. So within any of those cohorts, there are people that have very strong peripheral factors that are playing a role, that these are terms that have been used historically to merely indicate pain in a location of the body. So it sort of goes without saying that not all of that would have the same underlying cause.

But I think that's how the COPCs sort of came to be because we saw that these were clustering individuals; that they seem to respond a lot better to these central nervous system acting therapies, and that there was familial coaggregation. Not that these are all purely central problems because if you take any one of them and look at it, you're going to identify at least 20 percent of any of the COPCs in which there's a very peripheral phenotype, and another where there's an intermediate phenotype that's more regional pain, not fully widespread pain. So in any of the COPCs, it's probably only half of the people that have mainly central sensitization.

DR. KATZ: Well, in an effort to wrap up, do any of the speakers have any final comments?

DR. RAJA: I think the one comment -- what I'm hearing is, clinically, this is not a single disease; it's a spectrum of disorders. If you're going to study these patients, personally I think we need to somehow stratify these patients. And the question is what are the strata? Are they based on physical function in terms of number of pain states? Is it going to be based on psychosomatic comorbidities or is it based on catastrophizing or so? What are the different strata that are important in these patients? I think that's going to help us provide probably some more meaningful information.

DR. KATZ: Friedhelm, were you going to add something?

DR. SANDBRINK: Yes. I'm a little bit struck by what Dan just said. There are these 15 to 20 percent, even in our chronic overlapping pain syndromes, who seem to have pretty much isolated pain. I think maybe one particular aspect of how to move forward is truly -- and, Lesley, you articulated very clearly -- to come up with some kind of measure of how much centralized pain is present in this patient.
What is the degree of centralization? or centralized pain that is part of the component of some of these pain symptoms?

I think that that would help both for putting the patients into the right studies, I guess one as a predictor, but then also, I think it's part of an outcome I guess down the road as well. One reason why I feel it's so important is not just because we are talking about studies in these COPCS; we are also talking about all the other studies that happen, and I think, typically, this is not being assessed.

We do studies in low back pain and in diabetic neuropathy. We do a lot of studies, and often the component of centralized pain is not assessed, so we are missing on the correct phenotyping of all the patients, which I think has an impact on the success of the studies down the road.

DR. KATZ: Well, that seems like a good final comment for the morning. I'd like to thank the panel for participating and for their presentations. It's time for lunch.

(Appause.)
(Whereupon, at 11:45 a.m., a lunch recess was taken.)

As a couple of general comments, as all of you I think appreciate by now, Annie has been the rapporteur for this meeting. She's going to draft the manuscript, and you will all be invited to be co-authors on the manuscript; so that's just the way we do things. You don't have to be a co-author. You could send an email back saying I'd rather not be in author; entirely up to you.

We're going to be calling on the speakers for help with drafting certain sections because the presenters obviously had great expertise in certain areas, and we're going to run those particular sections by the speakers before we finalize the draft that we send out to the rest of you. Pain is almost always, if not always, the target journal.

The systematic review that Annie presented is separate. That will be a separate publication, a smaller number of authors, though the main manuscript from this meeting will refer to the...
I'll answer any questions before moving ahead in a second. As we go through the next couple of hours, I think there's an important thing that we've learned over the years, and that is that what we say in these manuscripts sort of can be put into three different buckets. Some of the IMMPACT publications are recommendations, recommended outcome measures for chronic pain clinical trials. Some of them are recommended considerations, the difference being, clearly, that there wasn't enough of a consensus to say we recommend the brief pain inventory for all clinical trials of chronic pain, and recommended considerations, obviously, is a softer kind of recommendation. We recommend that you consider using, for example, the BPA for chronic pain clinical trials. Then when we really wimp out, we can't get consensus on a recommendation or even a recommended consideration, what do we do? We have a research agenda. So for the rest of the afternoon, you should think about -- in terms of having the discussion proceed and getting done in two hours, we'll sort through as we distribute drafts and revisions, et cetera of the manuscript, whether we feel there's enough of a consensus to make a recommendation, or whether it's really a softer recommended consideration, or whether, for example, quantitative sensory testing really goes into the research agenda bucket, and we'll get to that, obviously.

Any questions about anything I said before I move forward? Dennis, did I leave out anything? (Dr. Turk gestures no.)

DR. DWORKIN: All right.

We tried to do our best to come up with an outline for the manuscript, and this is the outline at the 30,000-foot level, the proposed outline.

What you guys are supposed to do for the next two hours is to criticize this, amend it, and slice and dice it. So what we've left off, of course, is the first two sections are going to be introduction and methods, and that goes without saying. This is really the meat of the manuscript. The last section would be something like discussions and conclusions.

This is a proposal for the meat of the consensus recommendations, or recommended considerations, from this meeting. We're going to spend time talking about each of these sessions unless we run out of time; an initial section on the kind of meaty issues that we've been talking about throughout the last two days, central sensitization and centralized pain; mechanisms; types; the role of peripheral drive; descending inhibition and other spinal processes; and the brain.

I'll say something about terminology in a minute. We clearly could spend the next two hours, I think, talking about mechanisms and types of central sensitization and centralized pain. What I would like to propose is that for that initial section of the manuscript, that Annie -- and I'm going to respectfully leave Dennis out of this -- and I plagiarize the publications by Clifford and Dan that were background reading, and that we work with Clifford and Dan to finalize the two or three or four paragraphs of that section of mechanisms, types of sensitization, sensitivity, and centralized pain; unless -- we have enough people behaving like demagogues in this city, so I don't want to be another demagogue -- (Laughter.)

DR. DWORKIN: -- unless someone wants to say something more because we did run out of time at various panel discussions about this kind of challenging part of the article, and we obviously spent a lot of time talking about it this morning. But one way of moving forward is to kind of say let's leave it to Bob and Annie and Dan and Clifford to pull three or four, or however many paragraphs together, and we'll all take a look at what that looks like.

Raj?

DR. RAJA: Just a question. Does the quote/unquote overlapping pain syndromes come under the same bucket or is that a different bucket?
The issue is whether -- we've talked about these chronic overlapping pain syndromes. Is that part of the central sensitization bucket or is it a different bucket by itself?

DR. DWORKIN: Well, there could be an initial discussion here. I think it gets highlighted further down the outline, and we'll get to that. I have more slides.

DR. BRUEHL: Bob, I think that is kind of the distinction between the mechanisms and presumed markers of those mechanisms, right?

DR. DWORKIN: And we'll get to that.

DR. BRUEHL: Okay.

DR. DWORKIN: Any other comments? Yes, Mike.

DR. ROWBOTHAM: Mike Rowbotham. Is there going to need to be some sort of operational definition for when we consider sensitization?

DR. DWORKIN: Yes. Let's defer that to item number 3, though item 2 starts to bleed into it. I think we're going to have more slides.

DR. ROWBOTHAM: Mike Rowbotham. Is there going to need to be some sort of operational definition for when we consider sensitization?

DR. DWORKIN: Yes. Let's defer that to item number 3, though item 2 starts to bleed into it. I think we're going to have more slides.

What about this terminology thing? On the agenda for this meeting and throughout most of the last two days, we've talked about chronic centralized pain conditions. I think it was Raj this morning who suggested that he liked the word "syndromes" better than conditions. And I thought one of your slides, Raj, had an interesting -- the word "sensitivity" was used rather than sensitization. And I thought that was kind of interesting, too, because sensitization, to me at least, has a connotation of some active sensitizing going on, whereas sensitivity could be something you're born with.

So I think we have to make a decision -- this is something I'm not sure we can defer -- about what we're really calling either the condition or group of conditions that we're talking about in this article. One possibility is chronic centralized pain conditions, which was what was on the agenda. Another possibility, maybe a little bit more agnostic, is chronic central sensitivity syndromes, but this gets us right into IASP.

As many of you know, IASP has worked with the World Health Organization on ICD-11. And now, officially, in ICD-11, is my understanding, there is a diagnosis of chronic primary pain. So another decision that we have to make, I think this afternoon, is what do we all think about chronic primary pain? Is that what we're talking about?

One could imagine an reviewer of this manuscript saying, "What are you guys doing? We already have chronic primary pain."

This is how chronic primary pain is defined, and I mentioned this. I think we talked about this yesterday. Chronic primary pain is defined as pain in one or more anatomical regions that persists for longer than 3 months. It is associated with significant emotional distress or functional disability, and the symptoms are not better accounted for by another diagnosis.

I don't think that's what we've been talking about for the last day and a half. Does anyone --

DR. CLAUW: Don't you think that's what they meant?

DR. DWORKIN: They didn't say it, though. Yes, I do think --

DR. CLAUW: I strongly feel that's what was --

DR. DWORKIN: That is what they meant. Dan was reading my slides in advance over my shoulder because here's the evidence of what Dan just said. We could have easily prepared this exact same slide, which comes from a recent article in Pain, and instead of having chronic primary pain at the top, we could have had chronic centralized pain. It is what they meant. I think the reason we can set their terminology aside is there's nothing in it about central sensitization, central sensitivity, and all of those processes and mechanisms that we've been talking about for the
last day and a half.

DR. BRUEHL: Having worked with some of these IAS people before, my suspicion is they intentionally did not use that because they want to avoid implying mechanisms when we don't have any certainty that those are -- that's really what's going on.

DR. SCHOLZ: I was actually on the classification task force, and the decision was not to use mechanisms as a criteria for classification. So we are free to do with central sensitization, whatever we please.

DR. DWORKIN: Well, I feel like a decision has just come from on high -- (Laughter.)

DR. DWORKIN: I mean, wow! Thank you, Joachim. If Joachim thinks that we can go ahead, as we've been discussing for the last day and a half -- I mean, obviously, we have to put a sentence or two in the article saying why we're not using this -- I don't want to say what I think about it -- this bucket, and rather we're using centralized pain where we have some notion of mechanisms, we're going to have a sentence or two in it. There's going to be a chance that the article will get rejected from Pain because it's felt that we're defining a new pain condition that IASP has not defined, and we'll take that chance.

DR. WASAN: We're about to turn the somatosensory amplification term as sort of a process, and maybe that avoids some of these political pitfalls and gets away from identifying the mechanism per se, but it talks about it as a process that goes on that could involve these multiple other mechanisms.

DR. DWORKIN: Let's come back to that when we get to the phenotype because that's actually an interesting possibility.

DR. ROWBOTHAM: Right. So you could say we're talking about a subtype of chronic primary pain in the sense that we're insisting that there being some sensitivity or sensitization components, but that otherwise, including the overlapping pain syndromes, fit into this.

DR. DWORKIN: I love it. We're looking at a group of conditions within the larger umbrella category of chronic primary pain, where we have reason to think central sensitization or sensitivity is an important mechanism.

Simon?

DR. HAROUTOUNIAN: The only caveat might be that there might be conditions that do fit our criteria that are outside the chronic primary pain. So if we're thinking about neuropathic pain with central sensitization component, it falls outside this particular bucket. We just need to think whether we're just talking about a subset of this or a subset of maybe all sorts of chronic pain syndromes.

DR. WOOLF: I would argue very strongly that we don't lock ourselves entirely on the chronic side. Central sensitization, the most robust manifestation of it is, for example, post-surgical pain or the acute post-traumatic pain, where you get secondary hyperalgesia, et cetera, et cetera. They've locked themselves into chronic. There is an element of the involvement of central sensitization in chronic pain, but definitely in acute.

DR. DWORKIN: I'm all for that. I think we can easily, in the article, say that our examples or discussion will mostly involve chronic conditions, but that pretty much everything we say would also apply to a patient 7 days, 30 days after
surgery, trauma, shingles, et cetera. We need to change the slides.

Ian?

DR. GILRON: Just to chase that comment, in the possibility that there might be a phenotype of, call it fibromyalgia-ness, that predisposes to transition to chronic pain, maybe we could tie this in with prevention trials. It could be another area, but it might be relevant to --

DR. DWORIN: When we get to trial design, let's add that because that is not on the slide. Is everyone satisfied with how we've evolved in the last five minutes? Steve?

DR. BRUEHL: I am, and I'm just wondering if maybe in the paper it would be useful to have a Venn diagram with chronic primary pain and then chronic central sensitization syndrome, or whatever we call it, overlapping to some degree just to kind of show visually that we do think there's some overlap, but there are going to be conditions that aren't covered by chronic primary pain. I don't know if we want to highlight the IASP issue and all that.

DR. DWORIN: You took the words out of my mouth.

DR. BRUEHL: If we do need to, I think a diagram might be helpful.

DR. DWORIN: One of the other ACTTION groups is doing, and we've never done this before, a Delphi poll. It strikes me that your suggestion for that Venn diagram would be an impetus for Delphi poll to see how much of us agree with highlighting chronic primary pain, and how many of us think like let's just leave it aside. So we'll take that under advisement.

Dan?

DR. CLAUW: I think that is one of the most effective ways to leave it aside by doing what several people have just suggested and say central sensitization can occur in acute pain, in chronic primary pain, in all the other kinds of pain, but then we don't have to take on the controversy.

The only other thing I would recommend is, please, let's not us invent yet another term. If the term doesn't exist -- no one really uses the term, although I happen to agree that it's a good term, "sensitivity," like "chronic," or for that matter, "somatosensory amplification." We already have four terms that we have to live with in this field, and for us in IMMPACT to introduced yet --

DR. DWORIN: So that's a vote for centralized pain.

DR. CLAUW: I don't care which one. It's a vote against chronic central sensitivity because that doesn't yet exist -- people aren't writing about that.

DR. WOOLF: I would argue against centralized pain because that has a very specific meaning, is that it implies the autonomous, which may be just a small part of the whole package.

DR. DWORIN: And you like central sensitivity? Is that better, Clifford?

DR. WOOLF: That's better.

DR. CLAUW: Well, why don't we just use central sensitization? Why do we have to use a new term?

MALE VOICE: All pain is central. I mean, it just is.

DR. DWORIN: Mike?

DR. ROWBOTHAM: Pain with somatosensory amplification?

DR. DWORIN: We have like I think five different terms on the --

MALE VOICE: We'll never -- we can spend until 5:00 on this.

DR. DWORIN: I know. I know. Howard, can I call on you to get me out of this jam?

DR. FIELDS: I didn't realize that you were in a jam.

(Laughter.)

DR. DWORIN: I know. I know. Howard, can I call on you to get me out of this jam?

DR. FIELDS: I didn't realize that you were in a jam.

(DR. WOOLF: I couldn't agree more with Dan. The last thing we need is a new term. We've got more than enough terms.)

DR. DWORIN: So you would be happy with
something like central sensitization pain; nothing new about that.

DR. FIELDS: I like the idea of having a primary, well-established diagnosis, let's say fibromyalgia, or some other condition like interstitial cystitis with evidence of sensitization. Opposed to creating a new diagnostic entity that groups a bunch of things together, we take the entities that are already there and then say with or without sensitization.

DR. DWORKIN: All right. So I'm hearing three different possibilities, and maybe in the interest of moving forward, we just defer this as possibly a Delphi poll, or you guys will send me an email telling me what you think.

What we started with on the agenda is centralized pain. Another possibility would be central sensitivity, and the third possibility is just sticking with central sensitization as some kind of adjective qualifier.

DR. FARRAR: Just a very small point, which is that I think it's been pointed out several times, as Howard was just doing, that many of the comorbid conditions that we're looking at can have a centralized component or not. So I worry that calling it centralized pain suggests that there are two pains, and I don't think we want to imply that. So I would argue strongly for not calling it a pain separate from the other ones that we've got. Yes; I'm beginning to see the problems with that as well. I leave it to you. Never mind.

(Laughter.)

DR. DWORKIN: Thank you.

So nociplastic pain -- I'm sorry.

Sharon, did you have your hand up?

DR. HERTZ: Yes. Let's be careful that we don't use terminology that's going to get confused with central pain syndromes like thalamic pain. I just don't want this to start becoming --

DR. DWORKIN: We would have a sentence very early in the article that we're not talking about central neuropathic pain, for example, associated with stroke, spinal cord injury, multiple sclerosis. Yes, that's critically important.

Lee?

DR. SIMON: Just out of curiosity, if we do what Howard is suggesting, which is a nice compromise, it does eliminate the possibility that somebody might develop a chronic pain syndrome without being actually being able to be categorized based on vulvodynia with chronic, or chronic sensitization, or fibromyalgia with chronic sensitization.

For those people that think there might be a chronic pain disease and the right person can be stimulated by something else leading to afferent input that leads to chronic pain, you aren't living that as a possibility.

DR. DWORKIN: But I think that's going to be a thread throughout the article. As I understand it, there are some patients with fibromyalgia and IBS who don't have centralized pain, central sensitization.

DR. SIMON: Right.

DR. DWORKIN: There are more patients with OA who don't have that, but in both of those diagnostic categories, it can exist and it may not be there.

DR. SIMON: But turn it around. Is it possible that you had something that caused you to like what Clifford was referring to due to an acute pain syndrome. It's then gone, but yet, you still are having chronic pain. That's an independent event without -- it's possibly stimulated by some afferent input, but that afferent input is not there any longer.

DR. DWORKIN: Right, and that's the first bullet here.

DR. SIMON: Okay.

DR. DWORKIN: We're going to have a discussion --

DR. SIMON: Just want to be sure.

DR. DWORKIN: -- about the role of peripheral drive and that you can also have this in its absence. Absolutely.

DR. SIMON: Exactly.

DR. DWORKIN: That's that for bullet.
DR. BRUEHL: I'm thinking that given this discussion, it would be very helpful early on to explicitly state that we are not proposing a discreet diagnostic entity; that this is really more of a phenotype that's cross-diagnostic. That seems to be kind of what the discussion is.

DR. DWORKIN: Dan's raising his hand, but I'm hoping he's going to agree with you.

DR. CLAUW: I'm totally going to agree --

DR. DWORKIN: Terrific.

DR. CLAUW: -- and I'm going to suggest that we use the same kind of thinking that the RDoC in NIMH has used. In NIMH, six or seven years ago, they basically said we see these mechanisms that cross 10, 20 different psychiatric conditions, and instead of studying them as one-offs in between, we're going to look for these themes.

This would almost be like a central sensitization -- or whatever term, and I prefer that because I think it's the least charged -- can occur in acute pain, in chronic primary pain, but it's basically a mechanism that can be superimposed upon any other disease that we take care of. Then I think we stay away from some of the traps, where people are, because I think that really is what we're talking about. It can be in any of our pain conditions, in acute and chronic. It's never in all of them in any disease.

DR. DWORKIN: Well, and we call it central sensitization. If you and Clifford and Howard are fine with that, boy, anyone who isn't fine with that can leave for the airport early.

(Laughter.)

DR. FIELDS: That's kind of why I suggested what I suggested, which is we keep the diagnostic entities that we have and add in plus or minus.

DR. DWORKIN: Central sensitization.

DR. FIELDS: We're almost at a consensus. We should see how many people vote against that.

DR. DWORKIN: They can't. I'm not going to let them.

(Laughter.)

DR. DWORKIN: -- with postherpetic neuralgia maybe being the other end of the continuum.

MALE VOICE: You've to be on board, Lesley.

DR. ARNOLD: Yes, I'm on board. I was just saying, though, that you could actually even make the case that fibromyalgia is central sensitization, by a different name.

MALE VOICE: Not yet. I don't think you can make that case yet. It's possible.

DR. ARNOLD: It's possible.

DR. WASAN: I was just going to say we obviously could just put a qualifier on the fibro that is maybe redundant with the term "central sensitization." Then I would just, again, echo the research as the main criteria. You may even want to put a little more in the introduction about that, because that has provided very helpful and useful research agenda going forward.

DR. DWORKIN: I think that's a great idea.

I completely agree. I think it's a great idea.

DR. FIELDS: In agreement with that, it kind of gets around this issue of saying, well, here's
1. somebody with interstitial cystitis, and they have
2. a degree of fibromyalgia-ness. That's just a
3. little kind of convoluted way of saying what I was
4. going to say and what I think Lesley means.
5. DR. CLAUW: The advantage of going that
6. direction -- and it would be cool if we can agree
7. on this because it might be a little bit more
8. controversial. But then you could basically say
9. that negative affect is another thing that can span
10. a number of chronic pain conditions with or without
11. central sensitization.
12. MALE VOICE: And we know that's for sure.
13. DR. CLAUW: But that's for sure.
14. Catastrophizing can -- but I really think
15. it's -- the one thing that I probably feel the most
16. strongly about is don't have the core definition of
17. this include affect, include cognition, because
18. this is something that can clearly occur in people
19. that don't catastrophize, people that are not
20. depressed.
21. DR. DWORLIN: We're going to get to that.
22. DR. CLAUW: Right. But I think that RDoC

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1. thing does that nicely for us. If we say this is
2. the framework we're going to use -- like some
3. people with chronic pain have negative affect; some
4. have catastrophizing; some have central
5. sensitization, but we don't say that these always
6. occur together because they don't.
7. DR. DWORLIN: I love that. John?
8. DR. FARRAR: Clifford and I had a
9. conversation at lunch about the fact that there are
10. multiple mechanisms and other things that go on
11. here, but also about the fact that it seems to me
12. that what we want to define is that it's
13. sensitization of the pain relevant structures in
14. the brain. And I know that there's a big gray line
15. between that and other things, but what Dan's
16. talking about in terms of catastrophizing,
17. depression, et cetera, is more a limbic process, I
18. think. It's more a cortical interpretation.
19. I don't know how to divide those, but
20. somebody looking at this could say, well, central
21. sensitization, or essentially, everything is
22. central. Depression is central. This is central.
23. DR. CLAUW: Let me give you the reasons that
24. I don't think that's a good idea to do. I want to
25. first say that we are the only ones that wrote a

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1. DR. DWORLIN: I have a list of possible
2. aspects of the phenotypes definition, so let's look
3. at that when we get to it because it is exactly
4. what Dan's talking about.
5. Some of you that IASP has introduced a new
6. term, "nociplastic pain."
7. (Groans from audience.)
8. (Laughter.)
9. DR. DWORLIN: And this is pain that isn't
10. either nociceptive, as you can see from the
11. definition that I highlighted at the bottom of the
12. slide -- pain that isn't nociceptive, and isn't
13. neuropathic, and is still pain or something. And
14. clearly, Howard votes that we just not use the word
15. "nociplastic" in this article, and we make
16. believe -- we don't think it's relevant to what
17. we're talking about, and I'm happy to completely
18. leave it out of the article.
19. Dan?
20. DR. CLAUW: Let me give you the reasons that
21. I don't think that's a good idea to do. I want to
22. letter to the editor that said this is a stupid --
occurred over the last day and a half is like infinitely better than the IASP committees that get together by email or trying to work out some of these types of things. I think it would be really helpful to lay all these things out and just say nociplastic is one of the things that's been thrown out there, but then still say what we want to say.

DR. DWORKIN: Well, I think we all would be in your debt if you would write those 4 sentences for Annie and us.

DR. CLAUW: I'll write those 4 sentences. I'd be happy to write those 4 sentences.

DR. DWORKIN: And even 5 would be fine.

DR. CLAUW: Yes, maybe 5.

DR. DWORKIN: Does everyone agree we can move on from nociplastic pain? I see a lot of heads banging up and down. Okay. Let me just go back to the overview slide. I think we're done with bullet 1 of this outline. Does everyone think that we've taken care of mechanisms, types, central sensitization?

So one set of clinical trial objectives -- and we're really talking about efficacy, randomized clinical trials probably with phase 2 and phase 3 -- is to optimize the design of clinical trials of one or another chronic overlapping pain conditions by identifying a phenotype that needs to be examined at baseline in those patients, and maybe would be an inclusion criteria. We're not going to study you in our clinical trial of IBS unless you have the central sensitization phenotype.

Another way of thinking about, it seems to me, the clinical trial objective -- and this is a little bit more novel, and this has been a theme, too -- can we do a clinical trial where we enroll patients with one of several different either COPCs or other conditions that we've been talking about for the last day and a half, where we think central sensitization plays an important role in at least some reasonably sized minority of patients.

And Simon pointed out to me -- and I think this is true -- that we could even include -- actually, Simon's left. We can even click neuropathic pain patients here because we don't necessarily believe that all patients with diabetic peripheral neuropathy have central sensitization as their primary or predominant mechanism.

So that would be a trial that where it gets you randomized is having a phenotype, that we are going to define, irrespective of which of these kind of classic etiology based diagnoses you have.

DR. SIMON: Is the attempt of that design and carrying it out to develop a treatment for the phenotype or is it to develop a treatment for one of the specific causal events? Because I don't know how you develop a drug for a phenotype.

DR. DWORKIN: This goes back to Mitchell Max's -- he had an article in 1990.

DR. SIMON: That's right.

DR. DWORKIN: This is mechanism-based treatment. If you think central
1. Sensitization -- Mitchell thought if central
2. sensitization is an important mechanism, you are
3. going to treat patients who have that as an
4. important mechanism of their pain with some agent
5. that you think attenuates the sensitization. And
6. it doesn't matter whether you're diagnosed as FM,
7. or OA, or PHN.

DR. SIMON: So the purpose of that design,
9. as you've described it, is to develop a therapeutic
10. of some sort or another for the phenotype.

DR. DWORKIN: Phenotype mechanism, because
12. even earlier than 1990 Mike and Howard were talking
13. about segmenting, if you will, PHN patients into
14. one of three different mechanism-based groups, and
15. at least one of those three PHN groups had central
16. sensitization as a primary mechanism.

So no one's ever really thought this way,
18. that you could enroll a PHN patient, for whom the
19. mechanism of his or her pain was primarily central
20. sensitization, in the same trial as an OA patient
21. for whom -- that's why I said this is a very novel
22. approach.

A flip forward, just to illustrate -- and
2. I'm not a hundred percent sure about this. Lisa
3. LaVange, who is a biostatistician, who's head of
4. the Office of Biostatistics at CDER for 6 years,
5. and now she's at UNC, and Janet Woodcock published
6. an article about a year ago in the New England
7. Journal of Medicine on master protocols, including
8. basket and umbrella designs.

So I was thinking this is sort of like the
10. second bullet, right? Different diseases, and you
11. look at the patients with these different
12. conditions -- OA, postherpetic neuralgia, FM -- and
13. you phenotype them that their primary underlying
14. mechanisms of pain is central sensitization, and
15. you enroll them in this basket trial and treat them
16. with -- what would be the example? Duloxetine or
17. milnacipran, or some triple reuptake inhibitor that
18. we haven't developed yet.

Now, that's a very different approach. This
19. kind of basket trial, obviously, is a very
20. different approach than the first item here, which
21. is just optimizing the design of future IBS or FM
22. trials.

DR. WASAN: Maybe you want to add in a label
2. for sensitization as a primary or secondary
3. mechanism of the pain syndrome. For instance,
4. acute pain is a good example, acute postsurgical
5. pain. You could argue that the sensitization is a
6. secondary mechanism on top of the tissue injury
7. generated pain.

So that gives you more flexibility and
8. freedom, and it also gets to the same point of
9. sensitization is operative to more or less degrees
10. in a whole variety of situations.

DR. DWORKIN: I think I understand your
12. point, but that makes it complex because that
13. patient might have a kind of primary mechanism that
14. is not sensitization, so then you're treating a
15. secondary, presumably less important mechanism.

But that could still be making an important
17. contribution to their pain, so yes.

DR. WASAN: Well, that being the central
19. sensitization points.

DR. DWORKIN: Dan?
2. DR. CLAUW: I like both of those top two
3. things. So I hope we're not talking about these in
4. some way being mutually exclusive because I think
5. that they're both -- and I think the manuscript
6. could flush out because there are different reasons
7. that you would do the top bullet versus the second
8. bullet.

DR. DWORKIN: I was hoping you would like
10. both of them, because I think what makes the
11. manuscript better is that we talk about both of
12. these two very different pathways, optimizing and
13. then doing something novel that hasn't been done
14. yet, but it certainly seems possible, the kind of
15. mechanism-based targeted treatment. And this
16. slowly moves into biomarker-based treatment and
17. precision medicine. We're in that pathway.

Rick?

DR. MALAMUT: It's doable. We did this back
19. at AstraZeneca a hundred years ago, in which we
20. enrolled a population of patients who we believed
21. had mechanical hyperalgesia, and our tools, we were
using brush allodynia and punctate hyperalgesia. The tools may be more sophisticated now if MRI is ready or QST is agreed on, but it was doable. The key for us, though, would be -- if we go down this road in a phase 2 study, in which we're not studying FMS or PHN, we're studying a mechanistic base -- is, is that going to be a viable indication? So at least from my point of view, we would want to talk with FDA and say, hey, this is what we're proposing, an indication, and this is the study we're proposing. This helps because at least you're providing a way to do that. DR. DWORKIN: Obviously, I can't speak for FDA, but I think I can almost speak for NIH. Sorry, I'm going the wrong way. The NIH EPPIC-Net, the phase 2 clinical trials network that most of you know a lot about, they're very bullish -- from Francis Collins on down, they are very bullish about basket trial designs, umbrella designs, and master protocols in general. So even if this is not there yet for FDA, it's very close to being there for NIH. I'd be really surprised if there wasn't a phase 2 clinical trial of this design occurring within the next 24 to 36 months. DR. WOOLF: As you get rid of centralized. DR. ROWBOTHAM: So these designs are pretty standard in cancer therapy. DR. DWORKIN: Yes. DR. ROWBOTHAM: [Indiscernible - off mic]. DR. DWORKIN: In fact, the examples in the Woodcock and LaVange article are primarily oncology. A couple of other, pulmonary, I think. I may not be remembering that. I don't know that there's anything to discuss about the last two bullets. Jim mentioned pharmacologic in Richmond this morning, I believe, and I personally thought that was a really cool idea, designing a trial where you have an enrichment phase, and you identify the patients who putatively have central sensitization as a primary mechanism, and you might confirm it by seeing if they respond to a drug that you think targets central sensitization like milnacipran.

So I thought it would be kind of interesting to at least in the draft of the manuscript have a paragraph about the potential for pharmacologic enrichment, and we could also say something about enriched enrollment standard, enriched enrollment randomized withdrawal designs. IMMPACT's already been there. We've got articles, and there are many articles in the field about ERW designs, but there's much less in the chronic pain field about the possibility of pharmacologic enrichment. Nat? DR. KATZ: One of the bullets that's not there is whether we want to make recommendations related to central sensitization for people doing clinical trials who couldn't care less about central sensitization, but who's doing a regular old trial in chronic low back pain, or a regular old trial in osteoarthritis. We have recommendations for how patients should be characterized or potentially outcomes captured that would even make those trials more informative. DR. DWORKIN: So think about when you see the next slides about the phenotype outcome measures. I have more slides coming up about exactly those issues. DR. KATZ: It still feels like the outline is incomplete in that regard. If we are going to have a section on clinical trial objectives and designs, then we could have a subsection called clinical trial objectives and design issues in relation to chronic pain studies in general. DR. DWORKIN: Okay. That would be the third bullet on this slide. Raj? DR. RAJA: I'll just say, you're talking about pharmacological enrichment and central sensitization. Rather milnacipran, I would think ketamine as one of the probable drugs to test. DR. DWORKIN: Yes, definitely, effusion, whatever you know, yes, absolutely. Dan? DR. CLAUW: Just for completeness, and I think this is probably what Nat's getting at as well, I do think it's important to also say that even if you are not trying to identify the people with central sensitization, you may want to screen...
because you may want to exclude them. If you have a more peripherally-based target, you may want to identify the people you don't want to put in your subsequent trials because you see that there's a lack of responsiveness.

DR. KATZ: Yes. Wouldn't it be nice to know that you didn't have 80 percent of your patients in group A with central sensitization and 20 percent in group B with central sensitization when you're doing that, versus placebo?

DR. DWORKIN: So Dan, you would suggest if I'm going to do a trial -- I'm not -- of intra-articular hyaluronic acid for a knee OA, I should exclude the OA patients with predominant central sensitization because we can't imagine that HA --

DR. CLAUW: That would be exactly like a Samumed program, where I showed that this is an intra-articular injection, a Wnt inhibitor, that it works way better in the OA patients without widespread pain than it does in the --

DR. DWORKIN: So the third bullet on this side that we've just added, Annie's just added, is kind of Nat Katz and Dan Clauw's recommendation for other pain trials, and we'll get to this.

We'll have a paragraph at various places, that might be two or three paragraphs, about stratification, and we talked about stratification on and off during the meeting; stratified allocation when that's reasonable; stratified randomization, and we'll get to analyses, stratified analysis of subgroups.

So we'll talk about stratification. I don't know that we need to discuss it here. You'll see those paragraphs. That will be fairly straightforward. I'm a fan of an article that Tom Permutt, a statistician at the FDA, published about the different types of stratification about 10 years ago, so that article will be cited.

We talked about this. All right. This is my phenotype slide. Dennis and I tried to listen really carefully to all the wonderful presentations, and this is not, at this point obviously, meant to be a proposed diagnostic criteria for the presence of central sensitization, but it seemed to be the key things that people mentioned in their presentations and in the discussion.

Widespread pain as assessed by a body map, we've talked about that, Lesley and Dan; the history of multiple comorbid chronic pain conditions, and obviously one assessment approach would be the Maixner Williams screener that we heard about this morning; and disproportionate pain. It's not clear to me how you assess that, but it seems to me that there should be something on a physical exam that could give the evaluating clinician some sense of disproportionate pain that isn't QST. I don't know what --

DR. WASAN: There is [indiscernible] - off mic] validated things, the pain behavior indices. This goes way back to Waddell, but then it's updated with the PROMIS pain behavior scale. So there's a variety of identified pain behaviors.

DR. DWORKIN: I think that's patient report. How about a physical exam, Ajay? Is there anything on a physical exam that tells you, and Dan, and Lesley, and Raj, and Nat that the patient has disproportionate pain?

DR. WASAN: Well, you observe pain behaviors. It is an exam. It's not just self-report. Yes, you can have self-report, but you can observe those behaviors, and that's part of your exam. You document that.

DR. DWORKIN: Steve, and then Dan.

DR. BRUEHL: I was just thinking of the CRPS, we tried [indiscernible - off mic] in some way, and obvious would be the pinprick hyperalgesia and allodynia. I think Clifford mentioned that earlier I think in this context.

But Mike, I was thinking back to you mentioning a variety of traditional neuropathic pain conditions that are going to be associated with allodynia and hyperalgesia, yet you were arguing that they're primarily peripheral. It may cause problems if we include something like that in there, unless we're certain it's not really a peripheral [indiscernible] issue.
DR. DWORKIN: This is part of a multidimensional kind of phenotype. Dan, do you ever do pinprick with fibromyalgia patients?

DR. CLAUW: No.

DR. DWORKIN: Is there anything or do we delete this bullet?

DR. CLAUW: No, I wouldn't delete it. I think you could put something like signs or symptoms of allodynia or hyperalgesia. The symptoms include things like does it bother you if you wear tight clothing? Does it bother you to sit in a chair for a long period? Does it bother you if a blood pressure cuff's inflated? Those are symptoms that help discriminate.

Then if someone wants to go a little bit further and do like a clinical test, there have been a couple articles published of using a blood pressure cuff as a poor man's quantitative sensory test. It's in every exam room, and it's not a terrible thing. I'm not necessarily suggesting that people have to do that, but you could give a list of -- and you could say, even QST. You could say that signs or symptoms of allodynia and then in parentheses, here are some symptoms. Here are some signs. If you happen to have quantitative sensory testing, cool, you can do that.

I would leave it there, but just give people options about, given the clinical setting they're in, the degree to which they try to assess that. DR. DWORKIN: Does anyone disagree with disproportionate pain as assessed by signs and symptoms of allodynia and hyperalgesia, in which "disproportionate" is absurd on the face of it because if it's something that is a symptom or a sign of a disease, by definition, it's not disproportionate. So there's no need for that term. It's confusing, it's subjective, and it could be used to say, well, okay, this patient's pain is proportionate, so they don't have this condition. So I would just get rid of it. It's not as bad as nociplastic, but it's pushing it.

Howard? I agree with him. I just love the word "disproportionate," and I wanted to use it somewhere on a slide. But I think he's right. We don't need disproportionate with signs and symptoms of --

DR. CLAUW: [Indiscernible - off mic] -- and hyperalgesia; it's not disproportionate. It's the pain to normally non-painful --

(Crosstalk.)

DR. DWORKIN: This will be the easiest consensus of the year.

DR. FIELDS: The next bullet, sensory amplification, has all the correct aspects of what's implied by that term.

DR. CLAUW: Those are different. Those are symptoms. Those are surveys and symptoms looking at sensory amplification other than pain.

DR. FIELDS: Pain's not a symptom?

DR. CLAUW: I'm just saying that I think it's still okay to have that as a separate bullet point and say allodynia, all the different ways you might be able to assess --

DR. DWORKIN: Howard, this is the patient-reported questionnaire bullet, so signs and symptoms would be more in the history physical exam.

DR. RATHMELL: I would take signs out of it. There are no signs. What's a sign? It's symptoms of.

MALE VOICE: Symptoms based on the [indiscernible - off mic].

DR. DWORKIN: No, I know. I know. Let's defer until manuscript whether we remove the word "signs." But of course you're right, Jim, that it's all by patient report, even QST, so it's not really a sign.
DR. ROWBOTHAM: I agree with Howard on "disproportionate," that word. But something that should be brought up and flipped around is patients who have elaborated examinations, it could be collapsing weakness to minimal stimuli, elaborated gait, sensory loss, basically impossible, all those things that neurologists look for on neuro exams to see if you can really trust your examination. So if you see a patient with signs of elaboration on their exam, then you kind of just have to start all over.

DR. DWORKIN: That's something very different.

Howard, you won. Dan agreed to 4 sentences or so on nociplastic pain. Will you write those 4 sentences?

DR. ROWBOTHAM: [Indiscernible - off mic]?

DR. DWORKIN: Yes.

DR. ROWBOTHAM: Yes.

DR. DWORKIN: And it's really exclusion in some ways.

(Crosstalk.)

DR. WASAN: The other term for what he's describing is called exaggerated pain behaviors. This is part of a well-accepted terminology. Neurology may have a slightly different terminology, but it's the same thing I mentioned, and we should put it in there, not disproportionate pain, but --

DR. FIELDS: Exaggerated is more on the diagnostic side.

DR. WASAN: So just call it pain behaviors.

(Crosstalk.)

DR. WASAN: You just call it pain behaviors, and include all the things like Mike said.

DR. DWORKIN: I promise that you will get at least three or four opportunities to criticize what Mike writes. I promise.

DR. BRUEHL: It seems like some are arguing to include that as a criterion for this and others saying it's an inclusion. Which is it?

DR. DWORKIN: It's more an exclusion.

DR. BRUEHL: Okay.

What's your comparison?

DR. DWORKIN: How about I propose we wait and see what Mike comes up with.

DR. WASAN: Okay, fine.

DR. DWORKIN: We'll have 4 or 5 sentences from Mike, and we'll see whether the other individuals in the room agree with him.

The next bullet is really a bunch of questionnaires that patients fill out, and I just put down various ones that we heard a lot about over the last two days: The Pill, the ACR-90 Somatization Scale; the fibromyalgia survey that Dan and Chad Brummett use; the Central Sensitization Inventory; my favorite, Barsky Somatosensory Amplification Scale.

It's my favorite because we 30 years ago showed that patients with high somatosensory amplification scores, shingles patients with high scores are more likely to develop PHN 3 to 6 months later. But obviously, these are all measures that are assessing a kind of -- one imagines an underlying construct of somatosensory sensory.
amplification not only of painful stimuli, but as we've heard, loud noises, sounds, bright colors, odors, who knows what?

I don't know. I think, Steve, you asked this question that given all of these measures -- and it could have been a longer list -- are we going to be able to recommend one of them? And I think, no.

DR. BRUEHL: I actually had a comment on this, and I'm not familiar with all of these very well. But the CSI I know has been used quite a bit. My take on it from what was presented here, and my little bit of reading of the literature, is that those studies are heavily weighted towards fibromyalgia samples. I think the problem, probably in some of these other measures as well, is that that's probably also true.

I'm wondering, if we're talking about a cross-diagnostic construct, and we've shown that CSI is elevated in fibromyalgia compared to controls, I would really like to see, before we recommend a specific measure, evidence that some of these other overlapping pain conditions have the same elevations on this measure of central sensitization.

DR. DWORKIN: Well, we know TMD does. So it's not only fibromyalgia, it's TMD.

DR. BRUEHL: Well, the same cross-cutting. So maybe MAPP has this information, but I think that would help to be able --

DR. DWORKIN: I've got two samples of shingles patients for the somatosensory amplification scale.

I think what I'm hearing you saying -- I wasn't expecting anyone to say this, but maybe we really do need to think about somehow getting a systematic review done of sensory amplification measures, these and all the others we identify, with respect to how they were developed, what's their content, what do we know about reliability, validity, assay sensitivity in clinical trials, if they're ever used in clinical trials.

DR. BRUEHL: That would be a great use.

DR. CLAUW: And there are some studies now that are doing that along with doing QST for other non-painful sensory stimuli, which would actually then help say, okay, if we're really trying to get at some underlying biological construct, then the questionnaires that match up best with QST might be the ones that we gravitate to.

But I would agree with you. I think taking that and saying that might be useful to screen and put a couple of things. But again, our group hypothesizes that the people with central sensitization don't have chronic overlapping pain conditions don't have nearly as much pan-sensory sensitivity as the ones -- like an OA patient with central sensitization or an RA patient.

I think that's still an unanswered question, so I don't think we should -- as Steve's saying, I don't think we should imply as part of the construct.

DR. DWORKIN: I think Dan just made a proposal, which is the first three bullets on this slide would be -- and they obviously have to be rewritten -- the way we propose the phenotype is identified, and the bottom three bullets are more a research agenda, not only the QST or fMRI and metabolomics, but even which questionnaire would really add value.

Certainly, Dan you said a moment ago that fatigue, sleep, mood, cognitive abnormalities are not defining of the phenotype.

DR. CLAUW: If you look at the 2001 fibromyalgia measure that we've used a lot, that has two elements. It has a widespread-ness of pain, and the other, there's the fatigue, memory problems, and sleep disturbance. They each contribute about 50 percent variance in predicting poor outcomes to surgery, poor outcomes to opioids. So no, I don't mind in any way, but they're separate. They load on separate factors. That was the factor analytic paper of Andrew Schrepf, that someone presented this morning. They're separate factors, so you have to assess them separately or just say I'm not going to look at -- but what's been called space, or fatigue, sleep, mood,
cognitive, that's very well established to be part of this.

DR. DWORKIN: So you would move that up and say --

DR. CLAUW: Move that up, and then have the bottom two be sort of optional or research agenda.

DR. DWORKIN: Comments on Dan's proposal, that bullets 1, 2, 3, and 5 are relatively defining of the phenotype of central sensitization, and bullets 4 and the last one, obviously, kind of need further research. Anybody want to disagree with that, comment on it? I saw some hands. Mike?

DR. ROWBOTHAM: I just wanted to add to it, but I can wait.

DR. DWORKIN: Okay. Roger?

DR. FILLINGIM: I guess I wasn't thinking that fatigue and sleep and mood and cognitive abnormalities are part of this central sensitization. They may frequently accompany it. They certainly frequently occur in the absence of it, but I wouldn't put catastrophizing or any of those in the same bucket as things like sensory amplification, or whatever kind of pain this is. It's clearly not disproportionate or exaggerated, but some other kind of pain. I don't like the idea of these non-pain related symptoms being part of a classification of central sensitization that we're describing in the context of pain.

DR. DWORKIN: So you would consider those kind of frequently co-occurring but not in any way required as part of the phenotype; that you would say if you had 1, 2, and 3, that identifies the phenotype, and 5 frequently occurs in concert with the phenotype. Dan?

DR. CLAUW: I disagree because, again, we have data that that construct in the MAPP and in all these studies that we've done predicts a fair amount of variance. And if you look at cluster 3 in AFRA [ph], it's loaded with it.

DR. FILLINGIM: Yes, but predicting variance doesn't mean it's part of --

DR. CLAUW: Well, predicting variance and non-responsive as a treatment, so it is sort of -- that's more implying mechanism. It's not just showing a cluster, it's --

DR. FILLINGIM: Well low education level would predict responsiveness to treatment. Should we add that? I guess I'm just thinking, at some point, we're going to have all of the brain and the subjective life of the human in here, and we've moved pretty far from pain.

DR. FARRAR: It relates to what I said before, which is that I think the critical components, the depression, the catastrophizing, the justification, is part of the control that we exert over what we experience in the environment, but it's not what we're interested in studying here.

DR. DWORKIN: So Dan, if someone had 1, 2, and 3, but didn't have fatigue, sleep, et cetera, you would still diagnose them as having fibromyalgia, central sensitivity, right?

DR. CLAUW: Yes, except how often does that occur?

DR. DWORKIN: Right. So I'm thinking like someone with severe major depression often will have early morning awakening, but may not. So it doesn't define major depression, but it's almost always there. Is this sort of similar with the fatigue and sleep? It's almost always there in someone who has a predominant central sensitization --

DR. CLAUW: That's part of the criteria for major depressive disorder.

DR. DWORKIN: Well, it's --

DR. CLAUW: Sorry. But I -- (Crosstalk.)

DR. DWORKIN: Well, then you'd be going in a different direction; 3 from column A and at least 1 from column B. We could go in that direction.
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<td>2 DR. WASAN: I would support Dan because the</td>
<td>2 in a symptom complex. So you're using it to make a</td>
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<td>unique thing about these, and what's mentioned in</td>
<td>3 diagnosis. If you have it, it increases your</td>
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<td>that bullet point, is that many of those have been</td>
<td>4 confidence in the diagnosis.</td>
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<td>shown to be causal of central sensitization, not</td>
<td>5 DR. CLAUW: Exactly, and you're just helping</td>
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<td>just associated. We know that poor sleep and</td>
<td>6 people get more comfortable.</td>
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<td>experiments that induce poor sleep create more</td>
<td>7 DR. FIELDS: My guess is with the sleep,</td>
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<td>sensitization on QST and other measures.</td>
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<td>can worsen someone's mood, and you have worsening</td>
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<td>brain, and fMRI are those types of things. So</td>
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<td>there's a causal component here to sensitization</td>
<td>13 DR. DWORKIN: So could we do something? I</td>
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<td>14 mean this is sort of the DSM-3, 4, 5 model, that we</td>
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<td>15 list those four, the bullets 1, 2, 3, and 5, as the</td>
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<td>16 DR. DWORKIN: The other thing to think</td>
<td>16 kind of core features of central sensitization in</td>
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<td>about -- and Lesley didn't highlight it in her talk</td>
<td>17 chronic or acute pain patients, and that we kind of</td>
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<td>this morning -- but the ACTTION APT [ph] criteria</td>
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<td>for fibromyalgia, which was just published in the</td>
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<td>last couple of months, do highlight as part of the</td>
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<td>22 also -- fatigue and sleep.</td>
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<td>you will, of including fatigue and sleep in part of</td>
<td>2 abnormalities?</td>
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<td>the definition of a chronic pain condition. Jim?</td>
<td>3 DR. DWORKIN: I don't know what</td>
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<td>4 DR. RATHMELL: So why not just move it to</td>
<td>4 catastrophizing was, which is why I wasn't sure</td>
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<td>important coexisting considerations that will</td>
<td>5 where to put it. It is cognitive.</td>
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<td>affect response to treatment?</td>
<td>6 Raj?</td>
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<tr>
<td>7 DR. DWORKIN: No, that's what Roger thinks,</td>
<td>7 DR. RAJA: It's less likely to be effective</td>
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<td>but Dan and presumably Lesley disagree.</td>
<td>8 because widespread pain is an essential criteria,</td>
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<td>9 DR. RATHMELL: So even though it's uncommon,</td>
<td>9 so you have to have some criteria there, which is</td>
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<td>you would exclude any people who met the first</td>
<td>10 essential, and then you can have a secondary X of</td>
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<td>three criteria and didn't have the fifth there.</td>
<td>11 Y. There are certain which you really want as</td>
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<td>12 DR. CLAUW: Well, I guess I wasn't thinking</td>
<td>12 essential criteria.</td>
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<td>13 that the first three, that you had to have all</td>
<td>13 DR. DWORKIN: We could say you have to</td>
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<td>14 three in order to diagnose this because there will</td>
<td>14 widespread pain in two of the remaining three.</td>
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<td>15 be people that you don't even have all three. So I</td>
<td>15 Roger and then Clifford.</td>
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<td>16 was thinking that these were just more, if you see</td>
<td>16 DR. FILLINGIM: I just think conceptually</td>
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<td>17 this, this is supportive of the -- so maybe we're</td>
<td>17 there are several things on the list that we think</td>
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<td>18 thinking differently about how to -- because a lot</td>
<td>18 reflect central sensitization. That includes</td>
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<td>19 of criteria, you have to have column A plus B as</td>
<td>19 widespread pain, multiple comorbid chronic pains,</td>
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<td>supportive. And I'd be very okay with the B being</td>
<td>20 disproportionate pain, or whatever that is, and</td>
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<td>21 supportive, being fatigue, memory problems, sleep</td>
<td>21 maybe sensory amplification. The others don't look</td>
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<td>22 disturbance, and sensory sensitivity.</td>
<td>22 like they result from central sensitization. In</td>
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fact, Ajay was making the reverse case, that they cause central sensitization. That's an important distinction to me. What I'm thinking this list is about is if somebody is centrally sensitized, what phenotype does that produce, not what factors led to their central sensitization.

DR. DWORKIN: Clifford, did you have your hand up?

DR. WOOLF: I just think we're at risk here of defining central sensitization purely on the basis of fibromyalgia. Yes, that is part of the spectrum, but it's not the entire spectrum. Yes, there may be widespread pain, but, again, I go back to postoperative pain where it's not widespread, it's secondary. Hyperalgesia typically is in a limited [indiscernible]. I just think, yes, we got to capture the fibromyalgia for sure, but we've got to recognize that every feature that is present in fibromyalgia is going to be present in other clinical manifestations that include central sensitization.

DR. CLAUW: If we do that, and I'm okay with that, then we have to eliminate number 2, and put that over on the other side, because someone with osteoarthritis with superimposed central sensitization doesn't have COPCs. They got osteoarthritis. They developed central sensitization. I'm okay with that, but then let's just make sure that we put things in the right bucket. Then we'd have 1 and 2 as required -- 1 and 3 as required, and 2 and 4 as suggestive. But we can't have 2 as required because it doesn't occur in the people with OA or RA that develops central --

DR. DWORKIN: Is that our way forward, 1 and 3 required, 2 and 4 as frequently co-occurring but not required?

DR. BRUEHL: I mean, it's simply having one pain location with one additional one or not. I don't know what the answer is to that.

DR. CLAUW: That's a threshold for fibromyalgia --

DR. DWORKIN: For fibromyalgia.

DR. DWORKIN: All of multisite pain; I don't know. All of multisite pain! There was one other hand, and then we'll move on.

DR. BRUEHL: I'm sorry. We do 6 out of 9, that again, all these people with fairly constrained centralized pain, like OA, would not qualify.

DR. CLAUW: -- and a threshold for central sensitization.

DR. BRUEHL: I mean, it's simply having one pain location with one additional one or not. I don't know what the answer is to that.

DR. DWORKIN: All of multisite pain; I don't know.

DR. RAJA: Sorry. I'm just thinking back on what Clifford said, that we need to include the whole spectrum, and then if you use widespread pain in postoperative pain, it's not necessarily...
widespread pain. So even number 1 may not be an
essential criteria.

DR. BRUEHL: So postoperatively,
disproportionate pain would be the only thing you
could use to say somebody has central
sensitization, right?

DR. CLAUW: Or allodynia. Most of those
people do have some allodynia and hyperalgesia in
the region where they have chronic postoperative
pain.

DR. BRUEHL: That's what I meant.

DR. CLAUW: Yes, so you could use that other
thing, too. But yes, it wouldn't be widespread.

DR. DWORIN: We may have to carve out acute
postoperative pain and treat that a little
differently than all of the chronic pain
conditions.

DR. WOOLF: It's beyond the site of injury,
but not the whole body.

DR. CLAUW: Right.

DR. CLAUW: That's what's seen in a lot of
these people, though. It's spread regionally, it's
sensitized, but it's not fibro. It's not the whole
body.

DR. RAJA: No, but I can give the example of
postherpetic neuralgia, where patients have
allodynia and hyperalgesia. There is central
sensitization, but it's not widespread. It's often
dermatomal. So I think widespread may not fit the
criteria.

DR. DWORIN: John?

DR. FARRAR: No, go ahead.

DR. DWORIN: No.

(Laughter.)

DR. DWORIN: I talk only when you guys have
nothing to say.

(Laughter.)

DR. FARRAR: I'm wondering whether something
along the lines of the wider the spread, the more
likely -- the higher the likelihood of it. The
reason I'm bringing that up is --

(Laughter.)

DR. FARRAR: -- if you're interested

(Laughter.)

DR. CLAUW: When you see it -- for example,
in rheumatoid arthritis, the way we see it is it's
in areas that are not typically affected by
rheumatoid arthritis. There are certain joints
that are affected by RA and certain -- but I think
setting, although I agree that the acute pain --

DR. DWORIN: The same way we're going to
have two kind of pathways in terms of the type of
the clinical trial, we can also separate out to
some extent acute pain because there are different
issues. Mike?

DR. ROWBOTHAM: A lot of the protocols for
showing that there were sensory abnormalities
extending outside the area where you would expect,
based on the site of injury, those protocols have
been pretty well worked out. So there's lots of
literature that you can site showing how they
demonstrate that and how it responds to different
treatments. The same thing with postherpetic
neuralgia, there's enough literature that you can
say that it's spread beyond where it could possibly
have reflected the initial zoster reactivation.

DR. CLAUW: When you see it -- for example,
we can try to come up with something along those lines, that it's pain outside the distribution that you would expect to see --

DR. DWORKIN: Expected, yes.

DR. CLAUW: -- with that particular disease or injury.

DR. DWORKIN: And give examples; give these examples.

DR. CLAUW: Yes. It doesn't have to be widespread, but it's outside the distribution you would expect to see --

DR. DWORKIN: Examples from RA and PHN would be helpful.

Can we move on? Anybody? John, last word?

DR. FARRAR: Last word, disproportionately the last word. I think we need to be carefully, and maybe this comes up under your inclusion/exclusion section. To be clear whether we're talking about a peripherally maintained sensitization, if you like, the description of the injection of stumps from people who've had missing limbs, where the pain gets much better with the injection into a neuroma.

Some statement about needing to try to treat other things that to see whether it's, whether it's just the 20 percent who have RA, and RA pain all over the place, or who have arthritis, but it's arthritis in joints. So I'm wondering how to couch that, and I'm not sure what to do.

DR. DWORKIN: Well, the whole issue of whether there's peripheral drive there or not, we said we would talk about early on in the article because it's more conceptual. Is the question you're raising whether we need to think about that diagnostically, that we want to somehow partition this phenotype into those patients where there's some evidence of peripheral drive and those patients where the centralization, if you will, seems independent?

That wasn't the discussion I was hearing.

The sense I had was that we're not there yet; that if the patient has central sensitization pain, no one seemed to think it was critically relevant to do a clinical trial to figure out which of those patients have a peripheral component and which don't.

DR. FARRAR: What I'm suggesting is that at least there be -- not just at the beginning of the article but where we talk about the phenotype, that there be a sentence or two about that phenomenon so that people can be aware and maybe consider that in the --

DR. DWORKIN: Yes, we could put this decision in, something like why we're not requiring kind of interrogation of possible peripheral drive.

Friedhelm, sorry.

DR. SANDBRINK: I'm sorry. One last word.

Clinically, we often try to differentiate between multifocal pain or multisite pain where there's generalized pain; at least that's when I see a patient. So somebody who has truly what seems to be relatively localized headache, shoulder pain, neck pain, low back pain, but really not pain all over, at least in my diagnostic impression, I do make a differentiation for that.

suggested that instead of the word "widespread," that "multisite" might be a little better. Does anyone disagree with that, multisite instead of widespread?

(No response.)

DR. DWORKIN: All right. You made a decision.

Lesley?

DR. ARNOLD: I was just going to say that we looked at that question when we were developing the criteria and the different ways of defining widespread pain, and we learned that it can be easily defined as multisite, not just in the traditional 1990 approach, so the multisite was what we went with.

DR. DWORKIN: Exactly.

DR. ARNOLD: We were talking about defining widespread pain. I mean, it is on a continuum, so that's why I think you could put starting with beyond the site of injury up to the end of the continuum, again, fibromyalgia --

DR. DWORKIN: Right, is fibromyalgia.
1 DR. ARNOLD: -- where you have 6 out of 9 or
2 however you want to define it. So it is a
3 continuum, but at the very least beyond the site of
4 injury, if you will.
5 DR. DWORKIN: Maybe this really will be the
6 last word. Nat?
7 DR. KATZ: So multisite means 2 or more
8 sites?
9 DR. DWORKIN: There was a suggestion that, 10 yes, in some patients, it might only be one
11 additional site.
12 DR. ARNOLD: Like I said, on the continuum, 13 and then we have to decide where.
14 DR. KATZ: If you have osteoarthritis in 15 both knees, then you have multisite pain?
16 DR. ARNOLD: Uh-huh.
17 DR. KATZ: How about both knees and a 18 shoulder?
19 DR. DWORKIN: And presumably you'd have to 20 have a couple of others of these phenotypic
21 characteristics.
22 DR. CLAUW: In most of the big data sets

---

1 we've looked at, three is a better demarcation -- 2 DR. DWORKIN: Than two.
3 DR. CLAUW: -- to say that it's something 4 different because there are so many people that 5 have two sites of pain without having this process.
6 If you're counting sites, I'm not necessarily 7 advocating that, but if you're trying to set a
8 threshold, 2 wouldn't be central sensitization; 3 9 or more would be.
10 DR. DWORKIN: Saying like the cutoff could 11 be somewhere in the 2, 3, 4 realm -- 12 DR. CLAUW: And besides that it's a
13 continuum.
14 DR. DWORKIN: -- and that this is a research
15 agenda question.
16 DR. KATZ: So this is a requirement for the
17 identification of this syndrome or just one -- you
18 could central sensitization without multisite pain?
19 DR. DWORKIN: I think we said that 1 and 3
20 were required, and 2 and 4 were often.
21 I think what we're sort of dancing around is
22 whether this article is actually going to propose

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1 diagnostic criteria for central sensitization pain.
2 I think going into this meeting, none of us really
3 thought we'd end up with actually having to come up
4 with diagnostic criteria, because if we thought
5 that, we would have made sure there was some kind
6 of literature review of all of these bullets, which
7 we haven't done.
8 So I think we're going to have to figure out
9 one of two pathways going forward. We either
10 finesse this in the article by being a little
11 vague, by, as Lesley said, it's a continuum of
12 sites from zero to many, and we're not quite sure
13 where the best cutoff is, and it might depend on
14 the type of pain, et cetera. So maybe we could
15 finesse it.
16 The other path is that we have another
17 meeting where we actually prepare to come up with
18 specific criteria for the diagnosis for central
19 sensitization. I think this decision I don't feel
20 able to make right now, but we need to, as a group,
21 consider do we just finesse it to the greatest
22 extent possible we can or do we want to have a

---

1 meeting in the O'Hare Hilton? I'm on purpose
2 making this not very desirable.
3 (Laughter.)
4 DR. DWORKIN: So let's move forward.
5 DR. BRUEHL: I'm sorry. You mentioned this,
6 so I have to respond to it. Using the wording
7 "diagnostic criteria" creates problems because of
8 the multi-diagnosis issue. We're adding another
9 one that overlaps multiple --
10 DR. DWORKIN: Yes. I think part of
11 finessing this article might be to say that we want
12 to propose a way --
13 (Crosstalk.)
14 DR. DWORKIN: -- an approach for identifying
15 a phenotype.
16 DR. BRUEHL: Yes.
17 DR. DWORKIN: -- without it being specific
18 criteria because we don't have the evidence base to
19 propose specific criteria.
20 DR. BRUEHL: Isn't criteria for identifying
21 a phenotype? We just don't call it a diagnostic.
22 DR. DWORKIN: I agree, yes. Nobody
1. disagrees with that.
2. What?
3. DR. FIELDS: Agree strongly.
4. DR. DWORIN: I agree strongly, and Howard
5. agrees strongly.
6. I think this might be my last slide. We had
7. a lot of discussion this morning about medical and
8. psychiatric comorbidities. I thought the best way
9. of summarizing that discussion is we don't know
10. whether these are the droids we're looking for or
11. not, and it depends on the specific clinical trial
12. and its objectives.
13. I think in many cases these are the droids
14. we're looking for, and we want to know about the
15. effect of the treatment, not only on the index
16. condition phenotype but on some additional
17. conditions, but in other circumstances, we might
18. want to exclude those droids.
19. Unless someone disagrees -- and obviously
20. we're going to leave out the Star Wars quote in the
21. article -- I think we're going to say it really
22. depends on the clinical trial objectives and the

extent to which comorbidities are excluded, or
actually the other extreme would be to be made a
secondary target of the treatment valuation. Does
your treatment benefit the fibromyalgia but also
the IBS, and the tension type headache?
Does that seem a reasonable approach?
Because I think we'll be here all through the
weekend if we try to decide that we're either
studying the comorbidities or excluding them. I
don't think there's a right answer, one size fits
all.

DR. RATHMELL: Medical and psychiatric
comorbidities are common. Think about it.

DR. DWORIN: Exactly. So this is a
strongly recommended consideration. We're not
recommending to do or do not, but we think an
investigator has to agonize over how they're going
to deal with the medical and psychiatric
comorbidities.

DR. FARRAR: I think it might be useful to
comment on the fact that from an exclusion
perspective, the issue is whether the patient has

1. the capability to participate actively in a study
2. so that somebody who's psychotic and all that -- I
3. mean, my point is that there's going to be a line
4. in each of these that is going to result in an
5. exclusion.
6. DR. DWORIN: So for this bullet, number 4,
7. and for 5, what we really tried to highlight in
8. preparing these slides, is the issues that are
9. specific to central sensitization. Now, there's
10. there's a long list. Of course, we all know of
11. other inclusion/exclusion criteria, but this seemed
12. to be the one that was foremost in terms of its
13. relevance to the types of trials we're talking
14. about.
15. So let's dispense with bullet 6. I think
16. it's important for IMMPACT and ACTION to be at the
17. cutting edge, if you will, and to talk about things
18. that haven't been talked about in previous
19. recommendations. So the statisticians and
20. methodologists in our group will write several
21. paragraphs about estimands and modern approaches to
22. dealing with missing data, particularly given that

these patients might have higher rates of AEs than
other patients, and the right and wrong way to do
subgroup analyses and address multiplicity.
So I don't think we need to talk about 6,
unless anyone wants to, because it will be in the
article. It will be a section. It will be up to
7. date, state of the art. It will be different than
8. anything in previous IMMPACT articles. But in the
9. remaining time, and we have quite a bit of time,
10. what we do have to discuss is outcome measures. I
11. think we've gotten to, pretty much, every aspect of
12. recommendations or recommended considerations for
13. clinical trials, except our outcomes.
14. Raj?
15. DR. RAJA: Just a question on 4. I think
16. apart from just saying that medical and psychiatric
17. comorbidities can occur, based on my reading of the
18. literature and what I've heard is they may also in
19. some way influence the outcome or at least -- I
20. think that concept may need to be brought in; that
21. that needs to be considered.
22. DR. DWORIN: Right. And that does go right
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<td>down to the bottom of the slide because one could imagine a subgroup analysis, ideally prespecified, where you compare the patients who have multiple comorbidities with the ones who don't, and you would have had a prediction about which group the treatment would work better in; absolutely. There are things on all of the slides that are potential moderators of treatment efficacy, and we need to highlight that. Dan?</td>
<td>Dr. Clauw: One suggestion would be you might want to put catastrophizing under 4 because it fits probably better under 4 than it does where it was before. It was clumped next to sensory before, and that's not really where it belongs. Dr. Dworkin: I agree. Dr. Clauw: And this is really an RDoC thing. Any chronic pain patient can have anxiety, depression, catastrophizing that always has a negative influence on outcomes. It's nothing that is specific to centralized pain or central sensitization. So let's just say that it's being evaluated, but it's not --</td>
<td>Dr. Dworkin: And then, the sensory amplification bullet and the last bullet are sort of more we need more data, more research, and catastrophizing gets moved over to the next slide. Dr. Kleykamp: So history of multiple comorbid chronic pain conditions and this fatigue, sleep, mood, those are very important but not -- Dr. Dworkin: And we will come up with language, yes. Dr. Kleykamp: Okay. Dr. Bruehl: No, but we were talking about moving catastrophizing to fatigue -- Dr. Dworkin: To the next, yes. Catastrophizing gets moved to the droids. Dr. Kleykamp: All right. Dr. Dworkin: Okay. Outcome measures. I think this is my last slide; it is. Depending on how much time we spend on outcome measures is when you get to go home. (Laughter.)</td>
<td>Dr. Clauw: Can I suggest nixing the FIQR? It's a terrible outcome measure. Let me read a couple items of the FIQR in case you didn't know how terrible it was. &quot;Prepare a homemade meal, no difficulty, very difficult; vacuum, scrub, or sweep floors; lift and carry a bag of groceries; arrange bed sheets.&quot; Need I say more? It's a terrible outcome measure. It's only ever been used in fibromyalgia. It shouldn't be more broadly used for this construct. There's just nothing about it that is good. Dr. Dworkin: So Dennis and I do our very best to make everybody happy, so how about this? That we take the FIQR off this list, but we have a sentence somewhere in this section that given its long history of use in fibromyalgia clinical trials, that for a fibromyalgia trial, the investigator could consider it? Dr. Clauw: Yes, but that's different. I don't think that's really what we're talking about.</td>
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here, but that's okay.

DR. DWORHIN: NO, no, but that's the point of this list. The point of this list is for you to say what you said and for us to kind of deemphasize it.

DR. ARNOLD: Absolutely.

DR. DWORHIN: Okay. We've solved the FIQR.

DR. TURK: We dealt with this in the IMMPACT I or II, whichever one it was, which is when there are specifically identified measures for certain disorders, you should use those. When you don't have those is when you use --

DR. CLAUW: When you have a disease-specific functional status measure, you should use that.

DR. TURK: Yes, exactly.

DR. CLAUW: Above and beyond, perhaps a generic measure. I'm okay with that. Instead of calling out the FIQR and making it seem like --

DR. DWORHIN: That was my mistake, putting it there. The others are more general, administer the body map again and to see if the number of regions has decreased.

Whatever sensory amplification measure you might or might not have decided to use at baseline, give it again and see if patients are less bothered by mosquito bites; fatigue, sleep, obviously.

This is the point I think Lesley really made quite clear. If comorbidities are not exclusion criteria, then let's make some effort to see whether the treatment also has a benefit on pain intensity and maybe pain interference of the comorbid IBS, or TMD, or tension type headache.

Anything missing? So Dan wants FIQR off this list. Anything to add? Anything else to go off it? Howard?

DR. FIELDS: I was just thinking, do you think under outcome measures, it's premature to identify some as primary and others as necessarily secondary outcome measures?

DR. DWORHIN: I think what we'd say is something like for most circumstances, a measure of pain intensity for the specific condition being studied will be the primary measure, and that these would be secondary. A lot of sentences begin saying, "depending on the circumstances."

Clifford?

DR. WOOLF: Something potentially missing for research agenda is whether the presence of central sensitization represents a risk factor for chronicity or --

DR. DWORHIN: Yes. We should have -- and this would go in the research agenda section. I guess Claudia discussed this a lot, kind of the extent to which what we've been discussing, is there a risk factor for chronicity or a kind of risk factor for maintenance of the chronic pain longer than it would otherwise be? And that kind of transitions quite easily into prevention trials, which we haven't talked about, but I think deserves at least several sentences, if not a paragraph.

So risk factors for the acute to chronic pain transition -- which I think you all know, NIH has lots of money from a common fund initiative, to say, acute to chronic pain initiative. So there should be a paragraph in this article, and prevention follows on from that.

Steve?

DR. BRUEHL: I had a question about the pain intensity interference in comorbid conditions. So what we have is a phenotype that is cross-diagnostic, and part of characterizing that phenotype is to ask for pain intensity. And because it's, by definition, almost multisite, all you can ask is what's your overall pain intensity.

I'm thinking whatever we get as a pain intensity for the phenotype, and then we're saying now go to the individual components of that and ask for the pain associated with the individual components, I'm just not sure what that's asking.

DR. DWORHIN: Well, setting aside fibromyalgia, where I think it does get a little tricky, if you're doing a clinical trial of TMD and the primary outcome is TMD associated pain, you could also -- if I'm understanding Lesley's point correctly and if the patient has IBS, you could have them rate their IBS pain on a separate pain rating.
DR. BRUEHL: Yes, but what we're talking about is potentially a clinical trial where the entry criterion is meeting this centralized pain phenotype, so you'd almost have to have some pain criterion. I thought when it said impact domains, that that's what it was talking about, was the pain intensity associated with central sensitization phenotype.

DR. CLAUW: Just to make it [indiscernible - off mic].

DR. BRUEHL: Yes, please.

DR. CLAUW: You're looking at central sensitization in knee osteoarthritis patients and you're looking at the degree to which that resolves after knee arthroplasty. I know this well because we have a lot of these ongoing studies.

If you don't separately rate pain intensity at the knee and all the other places in the body, you can't tell if the central sensitization got better because people, depending on the rate at which their knee is healing, they're sometimes rating their knee pain, they're sometimes rating their overall pain, but you really have a hard time figuring out what their most severe pain is and knowing what got better with the intervention.

So in fibromyalgia, asking a summary measure is fine because people hurt all over, but we do a lot of work with these regional pain conditions like OA and RA, and if you don't ask the intensities at different regions, or at least big body region, 7 body regions, you really get in a lot of trouble afterwards because one part of the pain got a lot better from the intervention, but other components didn't.

DR. BRUEHL: So you don't even need a global pain measure in most cases.

DR. CLAUW: In something like fibro, I would use a global pain measure because that's how people tend to write their -- but even Lesley was talking about examples where the woman's rating or headache or whatever, and not knowing what to rate or things like that. I think that it is helpful just because we're into these studies, and you see so many different times where it's hard to know what the patient was rating.

If you don't collect that data -- and again, I think we don't want to do a map where we're rating 45 sites, but rating 7 different sites, we do that now, and it just adds like 5 or 10 seconds to the burden because it only comes up to rate if they check a site in that area of the body.

DR. BRUEHL: Or maybe we could make it just more clearer, because I assumed, when you were talking about having the impact factors assessed, that was a pain rating that in my head, I immediately thought, "Well, it's a central sensitization rating," which there really isn't one; I understand that. But I think maybe we need to be very specific.

DR. DWORKIN: Yes.

DR. BRUEHL: When you were assessing pain to identify this, you need to independently assess the intensity.

DR. DWORKIN: The reason I went back is depending on what kind of trial you're doing, an optimized trial of IBS, or of TMD versus the kind of basket trial where you might include in one trial patients with IBS and TMD and FM, the way you do your primary pain rating is obviously going to differ and meaning to say that. I think that's very important.

Any other comments about outcome measures? Raj?

DR. RAJA: Just a question -- going back to your, quote/unquote, "essential criteria," do the outcome measures capture those essential criteria?

DR. DWORKIN: I think they do. I know I looked at that at some point.

DR. RAJA: So you said 1 and 3 were going to be --

DR. DWORKIN: So we have to add, if allodynia and hyperalgesia are now specifically listed in 3, there should be a reassessment of allodynia, hyperalgesia also as an outcome measure.

DR. RAJA: That's where I'm heading. Thank you.

DR. DWORKIN: Yes, absolutely. Dan?
1 the last slide, the outcome measures, we should put
2 one of the options people could use that COPC
3 screener. You had it in a different place, but you
4 may want to map that forward to outcome measures.
5 DR. DWORKIN: Okay. Right. So basically,
6 we have to make sure that the outcome measure list
7 includes the baseline phenotyping measures.
8 DR. CLAUW: Right.
9 DR. DWORKIN: Absolutely. Chris?
10 MS. VEASLEY: I've been intentionally quiet
11 most of this meeting, but feel like I need to say
12 something around outcome measures. The pain field
13 in general has been very slow to bringing patients
14 into the process of developing measures. And like
15 Simone asked the question yesterday, do we know
16 what patients think is important with these
17 conditions? And we both have not done this for
18 individual pain conditions, nor have we done it for
19 people who have multiple pain conditions.
20 Particularly when it comes to outcomes, I
21 think in terms of research recommendations, that
22 needs to be added. There are some individual
23 efforts, like with the FDA in TMD, right now to
24 look at actually bringing patients into the
25 process, and actually asking them what's important
26 to them in terms of outcome measures, and including
27 that. But in terms of this as well, I think it's a
28 very important recommendation.
29 DR. DWORKIN: Thank you, because if there
30 were no other questions, the next thing -- are
31 there any other questions? Ewan?
32 (Laughter.)
33 DR. McNICOL: Sorry. You mentioned the
34 outcome measures, fatigue and sleep. If I remember
35 right, those were both outcome measures from
36 IMMPACT I and IMMPACT II. So are you suggesting
37 that we look at them differently or use different
38 measurements?
39 DR. DWORKIN: Right. No, if they're in the
40 IMMPACT I and II article, then I was just not
41 forgetting -- I mean, I wasn't remembering. That's
42 right. To the extent that they were recommended as
43 secondary, or depending on the circumstance,
44 outcome measures, that's really captured in the
45 first bullet. Thank you.
46 So it's about two 2:45, and what I was going
47 to say is we didn't realize that usually the last
48 thing we do, the second afternoon, is to spend 15
49 or 20 minutes talking about a research agenda.
50 Chris just mentioned getting some patient input, I
51 think not only about outcome measures but about
52 research design more generally.
53 So we could spend another 15 to 20 minutes
54 on coming up with a bunch of bullets for a research
55 agenda. We have some: risk factor or longitudinal
56 studies of chronic pain transition, prevention
57 studies, et cetera. The alternative is Dennis and
58 I could thank you all for participating, and you
59 could all send me emails with research agenda
60 bullets.
61 John?
62 DR. FARRAR: I think I was daydreaming at
63 the time and need to bring up just one other quick
64 issue, which is that you went over analysis as
65 though it were a minor point, and I realized that
66 we need to do lots of things.
67 I mentioned to you at the break that one of
68 the issues in the analysis is the assessment of the
69 effect and whether things are done as responder
70 analyses or other things. The reason that I bring
71 that up is that in situations where you have a poor
72 definition of the group that you're studying -- and
73 I would suggest that no matter how close we get to
74 understanding centralized pain, the likelihood of
75 defining the group we want is likely to be 50/50,
76 meaning that you're going to have 50 percent of
77 people who have what you're trying to have and 50%
78 percent who might not.
79 We don't know what the numbers will be
80 ultimately, but in every study I've ever done,
81 there are groups who have the capability of
82 responding and people who don't. All I would say
83 is that in the analysis component of this, there
84 needs to be at least a short description of the
85 fact that there are ways to approach data and data
86 analysis that improved the likelihood of
87 discovering or being able to find those smaller
88 groups as opposed to simply looking at standard
1 means and averages.
2 DR. DWORKIN: Maybe I misunderstood you.
3 Could you be more specific? What I'm hearing you
4 say now is that we phenotype patients, and
5 presumably into phenotype positive, phenotype
6 negative. But we don't do that with perfect
7 reliability.
8 DR. FARRAR: Correct.
9 DR. DWORKIN: So the fact that we don't
10 phenotype patients with perfect reliability means
11 that if we're looking for a phenotype by outcome
12 interaction, we're less likely to find it, and need
13 a larger sample size, et cetera. Then you said
14 there are ways to address that. For example, what?
15 DR. FARRAR: The issue is if you look at the
16 data as a continuous variable, and you have only a
17 smaller number of people who actually have the
18 phenotype, and never mind that there are three
19 mechanisms that could underlie the phenotype, then
20 you tend to wash out people who get dramatic
21 responses. In 20 percent of the patients, you get
22 a dramatic response. You may not see that.

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1 We've talked about this at other IMMPACT
2 meetings, and in terms of the analysis component of
3 this, instead of just estimands, missing data, and
4 subgroups, I think it's key that we refer back to
5 some of the other work that we've done in terms of
6 how to look at understanding the data in a way that
7 looks at the levels of responders and other things,
8 so that we don't miss being able to find small
9 groups of patients who have dramatic effects.
10 DR. DWORKIN: Sure. If what you're saying
11 is there should be secondary data mining attempts
12 to look to see if whether a subgroup of real best
13 responders can be identified; sure. But as you and
14 I know from going back 15 years, Pfizer has never
15 been able to identify demographic or clinical
16 predictors of who responds to pregabalin and
17 replicate it. It's not that there haven't been
18 attempts to say this works, but it's never been
19 replicated; and likewise, Eli Lilly with
20 duloxetine; and likewise, opioid; and actually in
21 psychiatry, likewise oral antidepressants.
22 So being able to identify and replicate a

1 predictor, a moderator, really, of treatment
2 outcome, I'm all on board with trying to do it, but
3 nobody's ever succeeded.
4 DR. FARRAR: No, no. I agree with that. I
5 guess what I'm saying is that one way of designing
6 a trial is to design it based on a continuous
7 measure with a mean value outcome. Another way of
8 designing it is to say I want to look for a
9 percentage of patients who have a clinically
10 relevant response; however you define that. It
11 increases the sample size, but it allows you to
12 identify smaller groups of patients who respond;
13 not preidentify them, but it allows you to get a
14 positive trial where sometimes you might need it.
15 DR. DWORKIN: ACTTION has a paper that I
16 think will come out soon, where we conclude, on the
17 basis of a bunch of pretty sophisticated analyses
18 that Omar [ph] spearheaded, the notion in the pain
19 field that response is bimodal, is an artifact of
20 the way in which those data were analyzed. And if
21 you analyze the data correctly, at least for
22 chronic neuropathic and musculoskeletal pain,
1 better and can be done, and maybe give you some
2 better -- it's a nice research agenda thing.
3 DR. DWORFIN: If something gets replicated,
4 I don't care whether it's in psychiatry, neurology,
5 or pain, I'd love to see the article. But yes, I'm
6 all in favor of doing it, absolutely.
7 Okay. Do people want to spend another 20
8 minutes on developing a research agenda or has
9 everybody had enough and wants to catch the nearest
10 Uber to the airport or the train station?
11 MALE VOICE: Bar.
12 DR. DWORFIN: What?
13 MALE VOICE: Bar.
14 DR. CLAUW: You can give the people that
15 want to say and go over the research agenda the
16 ability to do that.
17 (Laughter.)
18 Adjournment
19 DR. DWORFIN: I saw a lot of faces just
20 staring at me, but one very vigorous no. So on the
21 basis of the one very vigorous no that was kind of
22 let's get out of here as soon as possible, Dennis

1 and I would like to thank you all for your
2 participation. This was a great meeting. You will
3 be seeing this manuscript over and over again until
4 you're sick of it and us, and safe flights home
5 everybody, and see you at the next IMMPACT meeting.
6 (Applause.)
7 (Whereupon, at 2:53 p.m., the meeting was
8 adjourned.)
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