Sean Mackey, MD
There's never a dull moment in my world. It's always different. I think it's one of the key messages for anybody thinking about pain from a medical standpoint, a policy standpoint, an employer standpoint, is that everybody experiences pain to a given stimulus or injury differently. Everybody.

LuAnn Heinen
That's Dr. Sean Mackey, Chief of the Division of Stanford Pain Medicine. Millions of Americans are living with pain that disrupts their work, relationships, and daily lives. Many of them struggle to get clear answers, effective treatment, and even validation that their pain is real.

I'm LuAnn Heinen, and this is the Business Group on Health podcast, conversations with experts on the most relevant health and well-being issues facing employers.

Today, we're talking about why chronic pain is so difficult to diagnose and treat, what factors can amplify or alleviate pain, and elements of evidence-based treatment that may surprise you.

Dr. Sean Mackey, welcome to the podcast.

Sean Mackey, MD
Hi, I'm thrilled to be here. Thank you for having me.

LuAnn Heinen
We've been wanting to address the topic of pain for some time. But first, tell us how you got to be a pain expert.

Sean Mackey, MD
I always liked science and technology and I went into engineering early on and got a master's in bioengineering, a PhD in electrical engineering, but was always fascinated by healthcare. So I went to medical school, where I ended up becoming an anesthesiologist, attracted to the technology and the approaches of engineering and science to healthcare. But then along the way did a pain rotation and was fascinated by the unmet need we have in society of people living with chronic pain, and saw a way to hopefully impact this, and ended up training and going into the field where I've been for the last 25 years as a physician scientist.

LuAnn Heinen
You're at Stanford University, which has one of the larger pain management clinics in the country.

Sean Mackey, MD
We've grown by leaps and bounds. We're one of the larger academic, comprehensive pain management centers in the country, yes.

LuAnn Heinen
So how much pain are we collectively experiencing in this country, in the U.S.?

Sean Mackey, MD
Well, it is an astounding problem and I'll tell you that it's not just confined to the United States. It is a global issue. The best national data that we have is that about 24-25% of adults live with chronic pain and about 8% or so live with this concept of high-impact chronic pain, which is that pain that takes a significant toll on a person's activities of daily living or work. So it is a huge problem in society. The last economic data that we have suggests that it is a half a trillion dollar a year problem with regard to direct medical expenses, but then also indirect medical expenses, which are things like lost work productivity, absenteeism, presenteeism. It's just an astounding public health issue.

LuAnn Heinen
It really is, and just as an aside, I'm starting to feel a little bit like Chicken Little on this podcast because obesity is exploding, mental health issues definitely on the rise, eating disorders on the rise, we just did

chronic kidney disease on the rise, and pain. Let's talk a little bit about maybe there are some common drivers…the aging population, for sure.

Sean Mackey, MD
Yes and I think there's some common threads amongst many of these conditions, these chronic diseases. And chronic pain, you're right, we're all getting older, but on top of it, we're seeing more chronic pain because of our successes in medical care. We're keeping people alive from cancer that used to die. The problem is the treatments for cancer leave people with chronic pain. We're keeping people alive after trauma or in wartime, but the problem is they're often living now with unremitting chronic pain. The list goes on and on. It is, in a way, a victim of our own success, compounded by the fact that we are living longer.

LuAnn Heinen
In addition to what you said, 24 to 25% of adults struggling with pain at any point in time and then 8% with high impact, which you defined as what impacting their work and life activities on a regular basis.

Sean Mackey, MD
Yeah and for instance, employers, we're dealing with a massive productivity burden. We tend to think about chronic pain and people taking time off from work, absenteeism, and that's very much a real thing. That's a big part of that half a trillion dollar a year problem. But I'd submit that presenteeism matters even more. Meaning, yeah, people are showing up at work with their back pain, with their migraines, with their neck pain, but their productivity is way down and it's taking a huge impact on overall work performance.

LuAnn Heinen
You define chronic pain or persistent pain as lasting, what, more than three months?

Sean Mackey, MD
You know, there are different definitions for pain and that is one. Some people say three months. Some people say six months. I think the field has moved more and more into that pain which persists beyond the expected time of tissue healing. The reason for that is that depending on the injury you might get, you might expect the tissue to heal up pretty rapidly, and so if somebody has chronic pain that is for something that should heal up in a week, but they have pain that is a month or two months out, that's concerning. On the other hand, if your parent just had a total knee replacement, which is an incredibly painful surgery, and they're still having some pain several months out, we're not yet ready to call that chronic pain. Let's give that major injury more time before we declare it.

LuAnn Heinen
So why is pain “a product of the brain,” even though we perceive it somewhere in our body?

Sean Mackey, MD
We need to understand that the definition of pain is that it is an unpleasant sensory and emotional experience that serves as a protective system. Pain is not a simple readout from the tissues. It's not a simple thermometer, if you will, of the tissues. Instead, our nervous system, in particular our spinal cord and our brain, they integrate or sum all these signals coming in from the body. They add context to it. They add memory of past injuries and painful experiences. They layer on your mood, your attention, how well you slept, your level of stress, how much inflammation you have, prior life experiences, and it creates, overall, that experience of pain. That's why two people can have the same MRI, the same injury, and experience entirely different amounts of pain.

LuAnn Heinen
That is amazing that our body does that. Really quite amazing.

Sean Mackey, MD
It is fascinating. There's never a dull moment in my world. It's always different. I think it's one of the key messages for anybody thinking about pain from a medical standpoint, a policy standpoint, an employer standpoint, is that everybody experiences pain to a given stimulus or injury differently. Everybody. We have to take care in not projecting our own personal experience of pain onto other people because their

experience is much different. These are brain nervous system networks and all those nervous system networks that involve anxiety, depression, stress, your beliefs, all of those intersect with those circuits involved with pain and can amplify them or turn them down. They work both ways. What we have learned, for instance, when you mentioned surgery, we tend to think of surgery as this straightforward event and that whether you have pain or chronic pain afterwards is just dependent on the surgery and what we've learned is that what people bring to the operating room table, what they bring to that surgery, often has more to do with whether they have persistent pain or chronic pain afterwards than the surgery itself.

LuAnn Heinen
Are you talking about state of mind, attitude?

Sean Mackey, MD
State of mind and yes, yes. Also, levels of poor sleep, of anxiety, of depression, catastrophizing has probably one of the biggest predictors of whether somebody is going to have persistent pain, is going to be a poor responder to treatment. Catastrophizing is this fascinating term. It's a terrible term created back in the early 60s and it was made up, but what it means is that you tend to focus attention on the pain, you tend to amplify it mentally, and you can't get it out of your head. You ruminate repetitive thoughts and you feel like you have no control over your pain. That is a huge predictor for how people are going to do. We're now learning that in addition to these psychological aspects, we're now learning more and more about the role of social aspects. So social isolation, loneliness, play a key role in whether people are going to go on and have worsening pain or amplified pain.

LuAnn Heinen
So if some of these attitudinal mood, almost some behavioral differences, if they could be addressed pre-surgery, that could increase the prospects for a positive post-surgical outcome.

Sean Mackey, MD
Yes and this is where the field is moving. I got to tell you, I've been so impressed with many of our surgical colleagues for embracing this notion. If we had had this conversation 20 years ago, I would have been laughed out of a room. But now the surgeons themselves are recognizing that the state that the patient brings to their operating room table, that they need to be prehabbed, people need to get tuned up, if you will. The thing to remember about surgery, to put it in context, is surgery is nothing more than a controlled injury. It's no different than walking outside and getting hit by a car. The only difference is it's done in a sterile environment and you're unconscious. But that, in essence, you're undergoing a significant injury, preparing you for that injury and its course afterwards, that's where a lot of the research is going.

LuAnn Heinen
That's terrific. It sounds really hopeful that more could be done to improve pain post-surgery. We say pain is a product of the brain, but then we say it's not all in your head.

Sean Mackey, MD
Yeah, it's a nuanced statement that I have frequently fallen to. The reason why we want people to know it's not all in your head is we want to validate people's experiences. It's not all in your head, but it is all in your brain. The problem that we have faced for untold decades, if not hundreds of years, I mean, this is not a new phenomenon, is that people have always had this linear one-to-one association between the amount of injury, what you can see in the body and the amount of pain somebody should have. So if you can't obviously see the source of pain or how much damage, we tend to invalidate their experiences. We tend to say it is all in your head. We refer to them as histrionic housewives, as somaticizing. Women have taken the brunt of a lot of this on the pain front. Women tend to express more pain than men and seek medical care and as a consequence, there's a lot of invalidation and stigma. One of the things that I'm probably most proud about in my research, I've done a lot of work in functional brain imaging, is that we've been able to identify what are the brain circuits involved with that experience of pain, with changing pain. We've been able to, as a consequence, lend evidence and validation to those people that the pain, it's not in your head, but it is in your brain.

LuAnn Heinen
What are the mainline treatments for chronic pain?

Sean Mackey, MD
We can break it down into about six categories. They're as follows, the medications, the procedures or interventions, the mind body or psychological behavioral approaches, the physical rehabilitative approaches, what we used to call complementary alternative medicine approaches, and then lastly, number six is self-empowerment or self-education. With the medications, briefly, we now have over 200 medications that we can use for pain, the same number for the different types of procedures, everything from trigger point injections on up to spinal cord stimulation or peripheral nerve stimulation. Mind-body therapies have been exploding in the field with a variety of different approaches that help train the nervous system so people can take more control of pain. The physical and rehabilitative approaches to help condition the body, to help reduce what we call fear avoidance of pain. The complementary alternative medicine approaches, including acupuncture, mindfulness-based stress reduction and others. Then self-empowerment, which is, again, education. It's listening to these podcasts. It's reading about your health and it's putting the tools to action yourself. In the psych therapies, we think of cognitive behavioral therapy, and maybe you've come across that before in your other podcasts. It's been used extensively in depression, anxiety, and sleep stress. That is the foundation upon many of these behavioral therapies. Newer wave therapies are like acceptance and commitment therapy, emotional awareness and exposure therapy. All of these are targeting slightly somewhat different brain circuits. My partner, Dr. Beth Darnall, has encapsulated a lot of these into a single session called Empowered Relief, which takes the core components of cognitive behavioral therapy and mindfulness and instead of eight weeks of treatment, it's just one two-hour session. This is the kind of thing that's been implemented within workforce environments because it's just a one-off and it's been found to be as effective as 8 weeks or 16 contact hours of cognitive behavioral therapy.

LuAnn Heinen
What do you say to patients to validate their physical pain when prescribing a psychological treatment like, let's say, CBT?

Sean Mackey, MD
A lot of it is upfront education to help them understand the nature of pain. That what's going on in your brain is not a thermometer, but it is taking all those signals coming in from the body. Those signals have a name. They're called nociception. It's a Greek term, but it is the electrical signals from our peripheral nervous system that are registering injury. Those are being shaped by sleep, by stress, by anxiety, by depression. Those circuits in the brain responsible for our mood, for our stress, can be modified. They can be changed and they can be brought under one's control. I'll usually, in listening to people and talking with people, I'll listen for key words such as, you know, when I'm asking them about what makes their pain worse, they frequently will bring in stress. They'll frequently mention that their pain is worse Monday through Friday, and it gets a little bit better on Saturday and Sunday. I use that as an opening. Why do you think your pain is getting better on the weekend? And they'll say, well, I'm sleeping better. I'm not stressed as much. My boss isn't on my case. And I use those as to link then stress, anxiety, poor sleep, to their experience of pain, and then link that to skills that can teach people how to change their brain circuits so that they have better control of their stress, and then through that, their pain. Does that make sense?

LuAnn Heinen
Yep. That's great. Why are there so few drugs specifically for pain, especially in light of, you know, opioid concerns? I did hear you on Science Friday, on public radio, speaking back a year or more ago about a new category of pain drug that was approved, the first in 25 years.

Sean Mackey, MD
Yeah, yeah.

LuAnn Heinen
But it seems like we don't have a lot of pharmaceutical options.

Sean Mackey, MD
Interesting nuance here. We actually have a lot of pharmaceutical options. We have somewhat between 150, 200 medications that have been shown to have analgesic or pain-relieving benefits. I want to be clear,

you are right. What we don't have are many meds that are FDA approved for pain, anti-convulsants that have pain relieving properties, mood drugs that turns out work on pain circuits too, antiarrhythmic drugs that have pain relieving properties. But you are right. Very few pain-relieving medications. Suzetragine, the one that you probably heard me mention, was just FDA approved as the first in class as a new pain medication and we'll see what becomes of it.

LuAnn Heinen
That's an interesting strategy. So you did say psychiatric meds. Is there a big role for antidepressants?

Sean Mackey, MD
Yes. Medications that were FDA approved for depression or anxiety work on brain systems for anxiety and depression, but it turns out they can also separately work on brain and brain stem and spinal cord systems related to pain because they influence neurochemistries, compounds like serotonin, norepinephrine, dopamine. These are also common neurotransmitters used for modulating or changing our pain.

LuAnn Heinen
Yeah.

Sean Mackey, MD
That's one of the messages I have to give people. They're like, oh, why are you prescribing me an antidepressant when I'm not depressed? And I'd say, well, you're absolutely right. You're not depressed, but these medications will work on the same systems. They will work on brain and pain related systems. I think one of the key things to note, by the way, is of all these 200 medications or so that we have, very few of them work actually out on the periphery where the injury has actually occurred. Most of these medications work in the spinal cord of the brain.

LuAnn Heinen
I want to ask you about the placebo effect because there's been research on that done at Stanford and other places like Alia Crum and others and I've read studies showing that the enthusiasm with which a trusted healthcare provider offers a treatment has a big, big impact on how the patient reports it working and that's true for placebos as well as not placebos.

Sean Mackey, MD
Absolutely correct. This gets to that whole point that context is king or queen and that placebo is working through similar brain mechanisms as many of our other psychological treatments and even pharmacologic treatments. It is involving things like expectation, something called preconditioning, which is your prior experience with a particular treatment. In other words, if you took a prior treatment for pain and you expected it to work and it did work, you're now primed the next time. I'll tell you that the clinicians use the placebo response all the time through the power of their personality in influencing expectations. It is a very powerful influence. We're working to better understand how it works, why it works and whom it works and how to best use it to impact good outcomes without, by the way, we've got to be careful without being deceitful. That's the key. We can't deceive patients.

LuAnn Heinen
What suggestions would you offer to any listeners struggling with pain right now? I mean, how can we make the healthcare journey better and easier for people struggling with chronic pain?

Sean Mackey, MD
Don't suffer in silence. Seek help. Try to get in the hands of a good clinician who will listen to you, will validate your problems. If your pain problem is particularly complex, then get a referral to a good comprehensive multidisciplinary pain group. Be aware that there are a wide range of pain clinicians out there from those who are very procedurally interventionally focused that will tend to stick needles in you, to those who use more medications, and ideally get in the hands of docs who are going to look at you as a whole person, a very holistic approach and can apply these different, you know, multiple treatments. Get educated about your pain. The beauty is that there are a number of podcasts and other information out there that you can turn to to help learn more about your body, to learn more about what's going on in your pain. Interesting that there is a strong association between the level of health education a person has

and their pain, the chronicity of it, the persistence of it. Those with low health education do worse. So get educated.

LuAnn Heinen
Seek help. Get educated. Okay. What's on your research agenda? And then we've got a quick lightning round, but what do you hope to accomplish in this space in the coming years?

Sean Mackey, MD
Wow. Now you're asking a scientist to talk about their research. You got to put the brakes on me here if I go on. I want to address one problem around precision pain medicine. The fact that patients have to go through this frustrating, laborious trial and error process until they find something that works. We need precision pain care. To get there, we will need the development of models of individuals. It's going to involve developing biomarkers of pain that we combine with their self-report to characterize them and to build signatures of their pain. From that, my ultimate goal is to build something called a digital twin. A digital twin is a dynamic software representation of something that you can use to predict a future state. The first digital twin was Apollo 13. I know if you remember Apollo 13, where those three guys up in the capsule, they had a bad accident and it looked like they were going to die. But Houston, it turns out, had a separate capsule and a whole software program, they could model the capsule up there. So they created a digital twin. Well, that was the first, but it's now been used in industry and finance and now moving into healthcare, into oncology and cardiology. So my group, we're working on creating that in a human so that we can tailor these models to an individual patient. Now, the next piece of the research is to scale out what we're doing. Meaning, at Stanford and many other academic medical centers, we have all the resources to bring to bear that we would want. All of the medications, procedures, psychology, complementary medicine, rehab. Just look at California as an example, the fourth largest economy on the planet. Once you get off the coastal areas of San Diego, Los Angeles and San Francisco, it is a healthcare desert in this great state of California. That applies to a great amount of this country that people don't have access to quality care. So another part of my mission is I've started a nonprofit and we're spinning off the technologies that we've created at Stanford into this nonprofit to be able to capture high quality data, to be able to give these behavioral interventions at either no cost or low cost and make them available at scale, particularly to these underserved areas that are in need. It's to scale out that quality and make it available. So it's those two things and in truth, they intersect with each other at a final endpoint.

LuAnn Heinen
Wow, that is still really an ambitious, exciting agenda.

Sean Mackey, MD
Go big or go home, right?

LuAnn Heinen
What would be an early biomarker, an example of a biomarker for pain?

Sean Mackey, MD
Well, I actually published the earliest brain-based biomarkers of pain over 10 years ago. I bet against myself. I said, this can't be done. I proved I was wrong. And so we were able to create early brain-based biomarkers of pain. There's been some phenomenal work since then. We can now use it to diagnose the presence or absence of pain. We can predict a person's future state up to a few months out. There's a lot of things we can do with brain imaging. The problem is brain imaging doesn't scale and it's expensive.

LuAnn Heinen
Yeah.

Sean Mackey, MD
So what we're doing is layering in, I just finished a huge NIH grant to layer in high-density EEG, multiple blood tests, patient-reported outcomes, wearable data, and we're seeing some really cool signals about predicting future state.

LuAnn Heinen
Please tell me that for office-based assessment of pain, is there something besides like the smiley faces and the 0 to 10 or is that still the standard?

Sean Mackey, MD
Well, it's far too often the standard. We've spent this time together talking about how pain is a bio, psycho, social experience. It's the biological, it's the psychological, it's the social. The problem historically is that we all then distill that down into a single 0 to 10 pain score and we expect that pain score to represent the entirety of that bio, psycho, social experience and it does not. So where the field is moving and where I've been pushing it is to capture efficiently these other aspects of pain that encompass a person's life. And capture the degree of pain interference they have, capture how well they're functioning, capture their sleep, which is one of the most important things for people in pain, their mood. We can do all this now using computer-adaptive testing in a very efficient manner.

LuAnn Heinen
Okay, ready for a quick lightning round?

Sean Mackey, MD
I'm sitting down.

LuAnn Heinen
True or false, redheaded people perceive pain differently.

Sean Mackey, MD
Yes, true. There is some genetic polymorphisms that do influence redheads' experience of pain. It's subtle, but it's true.

LuAnn Heinen
Could they tolerate pain more easily or less easily?

Sean Mackey, MD
They tolerate pain a little bit more easily. They have a different response to analgesic medications. They tend to be less effective in redheads. You tend to have to use more of them. But again, we have to be careful about being binary. For the same reason that in general men are taller than women, I know a lot of women that are taller than men.

LuAnn Heinen
Okay, you're going to maybe say the same thing on the next one. Does gender make a difference? Women who bear children have a higher pain threshold on average.

Sean Mackey, MD
Actually, I don't know about those women who have born children. Isn't that interesting? In general, to experimentally evoked pain, women are more sensitive than men. To experimentally evoked pain. Now, what the heck does that have to do with an overall experience of pain? Nobody knows. It's also thought that women tend to cope with pain better, however.

LuAnn Heinen
True or false, genes play a role in our pain perception.

Sean Mackey, MD
They do, but it's overblown. Now, on one hand, if you ask a geneticist, they'll say it's 40% to 60% of the overall variance. If you ask a psychologist, they'll say 10%. It’s probably somewhere in the middle. It plays a role, but that's not where the answer is.

LuAnn Heinen
Okay. Imaging helps find the source of pain. All you need is an x-ray, a CT, an ultrasound, an MRI.

Sean Mackey, MD
Hard no. Imaging is used to verify what you have found in a physical exam and in a history taking. Imaging does not show pain. Imaging shows structure. Imaging shows function. The problem that we have are false positives, meaning somebody has a disc herniation with back pain, but it turns out the disc herniation has nothing to do with the back pain. On the other hand, there's false negatives, meaning somebody can have pain, you can get an image and you see nothing. Again, you have to remember they just show predominantly structure and they can miss things. It's not like Star Trek in the tricorder. We're not there yet.

LuAnn Heinen
Any favorite over-the-counter pain hacks?

Sean Mackey, MD
Good sleep is probably one of the best. Learn some breathing skills to reduce your sympathetic nervous system. Have a level of body awareness to reduce stress and tension. Those would probably be my first go-tos. There's a series of others we can go into.

LuAnn Heinen
Fish oil?

Sean Mackey, MD
If you're talking about over-the-counter stuff, there's some data on fish oil. There's data on something called acetylcarnitine, alpha-lipoic acid. These are all over-the-counter agents that in this country are sold as supplements. In other countries, they're prescribed substances, and they have been studied in FDA-controlled trials. There is some evidence around creatine. Creatine is the supplement du jour these days for maintaining muscle health, cognitive health, and there is actually data in pain. There are a number of supplements that have shown benefit for pain. I haven't come across any that hit the ball out of the park.

LuAnn Heinen
Vitamin C?

Sean Mackey, MD
Vitamin C is a good one to take before a major surgery, particularly a major nerve injury-type surgery. It has been shown to reduce the likelihood of developing neuropathic pain afterwards. There are some suggestions that taking vitamin C before or during chemotherapy can reduce the incidence of chemotherapy-induced neuropathies. Always, always, always, though, talk with your physician before doing any of these supplements in a surgery or treatment because they can influence blood clotting. They can influence the chemo actions because vitamin C is an antioxidant, and maybe your oncologist doesn't want you taking it. Talk with them first.

LuAnn Heinen
Dr. Sean Mackey, thank you so much for this. This was fascinating.

Sean Mackey, MD
Thanks. I really enjoyed the time. Great questions, and hope it's of help to you and the audience, and appreciate the opportunity to join you.

LuAnn Heinen
I've been speaking with Sean Mackey about why effective pain care requires understanding how the brain and body interact and expanding access to therapies that address pain from multiple angles, physical, psychological, and social.

I'm LuAnn Heinen, and this podcast is produced by Business Group on Health, with Connected Social Media. If you liked the episode, please rate us and leave a review.