Airing Pain 144: Dilemmas in Pain Research

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Edition features:

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Dr Kirsty Bannister, Neuroscientist and Associate Professor at Kings College London.

The interviews were recorded at the Annual Scientific Meeting of the British Pain Society, 2023.

Paul Evans

This is *Airing Pain*, a programme brought to you by Pain Concern, the UK charity providing information and support for those of us living with pain, our family and supporters, and the health professionals who care for us. This edition of *Airing Pain* was made possible thanks to the continuing support of the British Pain Society. I'm Paul Evans.

Dr Neil O'Connell

We still don't have great answers on *how* it might work, let alone *if* it works,

Professor Robert Brownstone

So, why do people have pain with, let's say, a lumbar disc herniation in the first place and the classical explanation is that it's pressing on the nerve. If that were the only explanation, then removing the disc and decompressing the nerve would alleviate the pain, but it doesn't.

Evans

This may be a daft question. How do you find a rat who has Parkinson's disease?

Dr Kirsty Bannister

Well, you don't. You have to induce it and that's the problem.

Evans

Questions, questions, questions. The more we learn, the less we seem to know. So, does today's breakthrough become tomorrow's dilemma?

The British Pain Society holds a scientific meeting each year. It's a major platform for pain management professionals, researchers, clinicians and industry leaders to come together to exchange insights and explore the latest developments in the field of pain.

The focus of one workshop in 2023 was the efficacy of spinal cord stimulators.

Robert Brownstone is the Brain Research UK Professor of Neurosurgery. He was one of three speakers who took part in the workshop. So, back to basics – what is a spinal cord stimulator?

Brownstone

Sometimes we try to help people who have pain with a treatment called ‘spinal cord stimulation’. That's a treatment where a wire is placed on the surface of the spinal cord and that pacemaker device is implanted and little

bursts of electricity are given to the spinal cord in order to try to treat the pain, to lessen the pain, and to improve quality of life. And so today, this afternoon, we had a symposium and I was speaking on – really on why we haven't made more progress with the treatment. It was a treatment that started in 1967 and we should be making more progress, and I put forward the idea that the reason that we're not is because we don't understand either pain or how the treatment works.

Evans

Well, the first question has to be – *does* the treatment work?

Brownstone

There's no question we can help some people with this treatment. I say that very definitively. That was certainly part of the debate today was how much of the response is a placebo response and do we have proper trials to show whether or not it helps patients.

On the other hand, what we all know is that we all have patients who have been helped tremendously by the treatment. Those are anecdotal cases for sure. We have – we *may* have – many of them, but we don't have the proper studies or enough well-done studies to show that we're really helping a lot of people.

Evans

That's quite surprising to me because I would have thought that a patient who is offered this treatment should really expect that it works.

Brownstone

So, we always tell people that we don't know whether it will work for them and people undergo what's called a 'trial of spinal cord stimulation' where they just have the wire sticking out of them, essentially sticking out of their body. And they try it for a couple of weeks to see whether or not it will be

helpful. If it is, then they get implanted. The question is, how will they be in a year or two or five years and we don't know the answer to that.

Evans

Just describe what the stimulator is.

Brownstone

So, it has an implantable battery that's like a pacemaker for the heart, but it's delivering shocks of electricity – instead of to the heart it's to the spinal cord.

Evans

And what do those shocks of electricity do?

Brownstone

That's an excellent question and one of the things I was talking about today is we don't really understand. Somehow they mask the pain or they 'gate' the pain so that people don't experience the pain – or not as much pain.

Evans

I'm just thinking about other pieces of equipment. I use electronic stimulations – a TENS machine. Is it the same principle?

Brownstone

So, some patients will tell us that this is like an implanted TENS machine. The principle of how it works is different, because TENS is just on your skin, and this is in your spinal cord. But that's definitely how some people will describe it.

Evans

What's your opinion on them?

Brownstone

My opinion is I see some absolutely remarkable effects that are absolutely not in everybody. In general, we would, depending on the reason why you're putting them in, but, in general, we think that we're helping about 70% of people – who we put them in, but I'm not sure that the number is quite that high.

Evans

70% sounds reasonably high.

Brownstone

Yeah. So that's the quote unquote, 'classical patient' who has had back surgery before and still has ongoing leg pain. That's what most of those studies would have targeted. The most common patient will be somebody who has had back surgery in the past, let's say, a lumbar disc surgery. And then, despite that, still have ongoing pain.

Evans

That ongoing pain, why is it ongoing?

Brownstone

So why do people have pain with, let's say, a lumbar disc herniation in the first place? And the classical explanation is that it's pressing on a nerve. If that were the only explanation, then removing the disc and decompressing the nerve would alleviate the pain. But it doesn't. It's called neuropathic pain because it's pain that has developed because of changes to the nervous system. So, there are changes to the circuits of nerve cells in the spinal cord and in the brain so that you experience pain and the question is, can we change those neurons? Can we change those circuits so that they are more normal and pain is less?

Evans

So, the cause of the pain might have gone, why does this still exist?

Brownstone

Well, we don't know the answer to that, but because these nerve cells and these circuits will have changed for some reason because of the pain and they're just not changing back when you remove the cause of the pain. So, most of the patients who we see no longer have an ongoing cause of pain.

Evans

Is it a last resort treatment?

Brownstone

That is very often how patients view it. It's a complicated question because, again, it depends on when they've come. Sometimes they come to us very early, in which case there might be other things that can be done. Sometimes they come to us very late and it really is a last resort and sometimes it's very clear that the treatment won't work for that particular patient and that can be, of course, devastating news because they view it as the last chance, that everything else has been tried.

Evans

That's Professor Robert Brownstone, and there will be advice for those considering a spinal cord stimulator implant at the end of this edition of *Airing Pain*.

Now, for many of us living with persistent pain or any long-term condition, we can feel bombarded with claims of that miracle cure, especially if your main source of information is the Internet. Don't forget that there are many trusted sites on the Internet. Organisations like Versus Arthritis, the NHS, the British Pain Society and of course, Pain Concern, who offer a wealth of information reviewed and rubber stamped by leading healthcare professionals and researchers.

But assuming we've left the worldwide virtual consultation room and we're back in reality with real clinicians, how do we know that the treatment they're recommending a) works and b) is the best option? What are the checks and balances going before a treatment or procedure becomes accepted?

Cochrane is a global independent network of health practitioners, researchers, patient advocates and others who review research findings to provide a more precise estimate of the effects of an intervention and to reduce uncertainty

Neil O'Connell's background is in physiotherapy. He's a reader at Brunel University London, where he's involved in research and teaches healthcare and allied professionals research methods and evidence-based practice principles. As a researcher, most of his work is around the safety and effectiveness of interventions for persistent pain.

He was the Co-ordinating Editor of Cochrane's Pain and Palliative and Supportive Care group, whose role was to produce Cochrane reviews of the effectiveness and safety of a range of interventions for acute pain, chronic pain, headache, migraine and palliative and supportive care.

He was also part of the British Pain Society's Efficacy of Spinal Cord Stimulation Workshop.

O'Connell

So, a Cochrane report is a form of systematic review and a systematic review is essentially a piece of research in and of itself, where we ask a specific question. For instance, it might be as I've just been speaking about at the conference today, what is the effectiveness and safety of implanted spinal neuromodulation interventions for people with persistent pain.

And what we then do is we systematically review all of the clinical trials in that space. And according to a pre-specified protocol, we try and organise

the evidence, critique it from a perspective of having a look to see what the risks of bias are in that evidence and try to draw conclusions with varying degrees of certainty about the answer to that question. So, Cochrane reviews, I think, are widely considered to be very high quality from a methodological perspective. They have their critics that we may be a bit methodologically pure and too rigorous. In many ways Cochrane wrote the book on how to do systematic reviews and I would like to think we maintain very high standards.

Evans

So, would I be right to think that you're the sort of overview? The last point in the chain to see that this is worthwhile and it's working.

O'Connell

I'm not sure we're quite the last point in the chain. I think we produce a form of evidence that is closer to a piece of evidence that should be informing clinical practice. For instance, if we roll all the way back to pre-clinical work. But I guess if we think about that semi-permeable membrane between research and practice, the next stage after us would be regulators, guideline developers, policy makers.

What we do at Cochrane is we summarise the evidence, we hope, in the most objective way and then we present that evidence to the community. But there is probably another step. Now I would say that clinicians should be able to rely on Cochrane reviews to give them answers to guide their practice. But Cochrane reviews purposefully stop short of making clinical recommendations. We summarise the evidence. What people do with that information, that's a further step.

Evans

Ignore us at your peril!

O'Connell

[Laughs] Well, I mean, I think people *do* ignore us and I think, like all evidence, people love evidence when it speaks to their biases and they find evidence threatening, opaque, difficult or frightening, if it challenges a dearly held world view, and that could be, you know, financially driven, it could be about professional identity, or it could be from the patient perspective of someone who really feels that something might offer them promise. I think that's the great challenge of evidence-based practice in many ways – we can create evidence, we can synthesise and communicate evidence, but I think the pandemic taught us that interpreting it, that's about values, and it's inherently political, and that's where it gets difficult.

Evans

And things that might have looked sensible pre-Covid – during Covid actually perhaps didn't look quite so sensible or vice versa.

O'Connell

Well, I don't know. I think it depends on who you ask. I mean, I was in a conversation because Cochrane are very in – in the midst of a controversy about a recent review on the effectiveness of masks for infectious diseases.

Now I think you could probably tell more about the way someone would vote in a national election from their position on masks than you can about the evidence for whether masks do or don't work. And it's a really good modern. contemporary example of how hard it is to do evidence. We like to think, 'create the evidence, act on the evidence', but the problem with all of that, of course, is in the middle of that are people. And people are interesting.

Evans

So, what were you telling the great and good at the British Pain Society meeting this morning?

O'Connell

I was part of a workshop, talking to the evidence for spinal cord stimulation in persistent pain. So, my talk was around the evidence. What is the evidence that it is efficacious, that it works specifically for the reasons that we think it would.

And what is the evidence that it's effective, i.e. that it improves outcomes when you compare it to something pragmatic like conventional medical management?

Evans

So does it?

O'Connell

Good question. It's an interesting picture. When we look at the question, sort of the efficacy question – does this intervention work compared to placebo? Does it work, you know, for specific mechanisms? What we find is a handful of small studies, all at really quite high risk of bias. And the answer from all of those studies is 'maybe/maybe not'. It really is very highly uncertain. When we look at studies that have compared spinal cord stimulation to usual care, so the – the design might be that you randomise people to get spinal cord stimulation plus conventional medical management – medication etc., versus conventional medical management alone – then we consistently see quite large effects on pain, on quality of life. Now the issue is because these are unblinded trials – so, we don't know what's driving those large effects and the other issue is the trials are largely dominated by industry sponsored studies.

That means that you get access to *some* of the information that you might need, not necessarily *all* the information that you might need. So, I think it's a really interesting question when you have large effects compared to usual care, and no compelling evidence of benefit over placebo. But, to be very clear, it doesn't mean that we know that it *doesn't* work better than placebo. One of the key thrusts from all of the speakers today was that what we

really need is larger, better industry independent studies compared to placebo.

But, as some of the scientists in the room were telling us, it's really challenging to get the money to do those, and they are technically very challenging studies as well.

Evans

With all the things you've said, the money and the technical challenges, how do you remove that bias?

O'Connell

Well, the technical challenges, it's about recognising them and trying to mitigate them as far as is reasonably possible.

The industry challenges – well – in an ideal world, the industry would share their technology. At no cost to them potentially because funders like the NIHR would fund the trial and all of its additional costs, and one of the challenges there is that doesn't consistently happen. And so it's very hard to pull the trial to be completely independent. And there was an anecdotal example in the workshop – I don't know if this is true so, there's my disclaimer – that the industry will not *always* allow independent researchers to have access to all the tech that they would need, its proprietary technology, in order to conduct those studies. So that's a problem as well. And one would have to ask the question, what is the industry's motivation for *not* wanting to co-operate in that way? Is it because the results from the control studies that we've seen so far have been relatively disappointing? Or is there some other reason? But we can only speculate as to what that reason is.

Evans

So, the role of Cochrane is actually to see through all these different things that might affect or might *have* affected a trial?

O'Connell

I think the role of Cochrane is to try to produce the least biased answer to the question. That doesn't mean looking for trouble? That just means forensically examining the evidence ecosystem that speaks to that question in order to understand the various influences at play and we have very long-standing and developed methods for doing that.

Our job isn't to attack – and I think sometimes people do feel that Cochrane reviews can be a bit of an attack or threatening – our job is to try to produce the least biased estimate. In terms of the industry aspects of that, Cochrane probably has one of the strictest conflicts of interest policies of any publication.

Evans

Neil O'Connell.

Staying with research, Kirsty Bannister is an Associate Professor at King's College London, where she specialises in neuropharmacology. She runs a research group exploring the molecular mechanisms that underlie different pain states and, importantly, to dive into the mechanisms of pain processing in health using animal models. So why animals?

Bannister

So, often we're trying to spot signs of dysfunctionality, but actually, if we don't know how the pathway should process normally, how can we know when there's something abnormal? So, we do a lot of work in healthy animals to understand the intricacies of different pain circuits and also then we translate that to the human scenario where we use healthy human volunteers to use identical paradigms to elicit pain and understand how individuals respond to those. And then when we have answers to the questions we've asked in health we move to disease and so we have animal

models of chronic pain and we have different patient populations who we apply the same test to and try and work out what's different.

Evans

How does chronic pain manifest itself in an animal?

Bannister

Obviously, the animals can't talk to us and tell us they're in pain, so we have to infer pain-like behaviours, for example, and anxiety-like behaviours, depression-like behaviours. So animals who are in pain, if you just observe them in their natural environment – in the home cage, they will have more distance between their litter mates than a healthy animal. They'll stick to the periphery of the cage. They won't use their cage enrichment 'toys' if you like, so much in terms of the tubes, and they won't burrow into the sawdust, they groom less. And then if they have, for example, an injured paw, they'll guard, they will show flicking tendencies of that injured paw, for example, and actually if they do have an injured paw, they'll groom that paw a *lot* rather than theirselves, so we can infer all kinds of ways, behaviourally, if the animal seems to be in a pain-like state.

But actually, a large portion of what we do is measuring neuronal responses. So we go straight to the cause of the problem, I guess, and we measure responses in the spinal cord and we have a look at how those neurons are behaving, because if they're behaving in a manner which is, they're firing lots of action potentials, that's telling us that there's a lot of activity in a certain pain processing pathway that then allows us to think about – mechanistically – how that might link to the pain that they're experiencing.

Evans

So, the changes in the neuron pathways – are they a result of the pain or do they cause the pain?

Bannister

Yeah. Again, that's a really good question. So, in the first place, if we ligate a nerve, for example, because we want to induce an animal model of neuropathy, that itself, that trauma to the nerve of a primary afferent fibr that is coming into the central nervous system will itself cause an increase in the number of action potentials that are driven. And then that's going have an impact on the second order neurons which are in the spinal cord for example. And now they're going to fire more so then when that happens, the brain is being told that there's extra pain signaling going on in the spinal cord, and so then the brain is going to try and act to send these modulatory controls back down to the spinal cord to inhibit processes. But in chronicity, those modulatory pathways don't work very well. And so they actually end up facilitating spinal neuronal responses that are already facilitated and so you get this amplified effect where the system goes into overdrive, if you like, and that really underlies hyperalgesia and hypersensitivity.

Evans

Relating that to humans to – to me and you, somebody with chronic pain, me with chronic pain. Pain signals are amplified in a certain way. Even though there's no stimulus.

Bannister

Yes, and that's what underlies spontaneous pain, for example, you know, individuals will often complain that they'll just be sat watching TV, and they'll get these shooting pains and they wonder why, because they weren't doing anything. But actually, your neurons are in a heightened state of activity, which means that they will fire with no stimulus to the peripheral receptive field and those are the pains that can be really quite disconcerting for patients because they feel like they're in a protected environment, sat in the armchair at home, not doing anything. And so then it's a struggle to understand, well, ‘why am I still experiencing these shooting pains’, for example, and that spontaneous pain.

Evans

Now chronic pain is a biopsychosocial phenomenon. The bio being the biology. I guess the psycho being the mind, the social being, everything else that's affecting your life around you. I mean, how can you apply that to animal subjects?

Bannister

We have to acknowledge that it's not a clear translation when we're looking in animal models.

We can, to some extent, understand whether social factors influence pain in animals and if you know, if we house them individually, they really don't like that. That will have an impact on these inferred pain behaviours, for example. But ultimately we can't model divorce or, you know, a long history of depression, necessarily in animals, or, you know, a childhood trauma. I mean, there are some models of that, but all of these things have to be taken into account when we have the adult patient in front of us who's experiencing pain. And actually, we really need to understand their emotional past to get a handle on the manner in which they're perceiving their pain and we can't model that in animals, which is why we talk about mechanistic underpinnings from animal studies. But we have to be really careful about quite how translatable those are when you think about the additional factors that influence pain perception in humans.

Evans

So, in some ways, animals are good subjects because you can ignore some of the social and the psychological factors.

Am I right?

Bannister

We would hope we're not ignoring them entirely and we *can* do experiments that allow us to manipulate effect in animals. It's *just* that we can't get them to talk and so we can't understand how they are feeling that day, how their pain has been the last week and we have to take all those things into account when we're thinking about the patient and how the pain is impacting their life and we just can't do that with the animals.

Evans

Kirsty Bannister. Well, she was the winner of the 2023 British Pain Society 'Patrick D Wall Award'. And she gave a lecture entitled *The Top Down Control of Pain in Health and Disease from Bedside to Bench.*

Now for my mind, 'Bedside to Bench' is the opposite direction of travel I would have expected. Surely research starts at the lab bench and ends at the bedside, doesn't it?

Bannister

People often think about forward translation in terms of human and animal research. You want to forward translate their findings, but actually more and more, it's clear that it's the backward translation that provides the better information in terms of, 'let's understand from the patient what their experiences are and understand how they're perceiving a certain painful stimulus' and then back translate that to the animal domain where we want to build better animal models. We really don't have great animal models of chronic pain and it's the same in neurodegeneration, you know we're trying to understand molecular mechanisms at the bench, but we don't actually have a very coherent animal model. So, I think backward translating observations from patients to animals is really important.

Evans

That's really interesting because you know what you're saying is that starting with the animal and ending with the patient is not necessarily the

right direction to go. The patient is here and now. What has gone before that is causing this?

Bannister

Yes, a classic example would be Parkinson's patients. We've spoken about that before.

The results that we're slowly getting out for the Parkinson's UK funded work we do has shown that there's a really distinct noradrenergic sub-type in terms of patient cohort. And for me, if I were to move forward and maintain the research in Parkinson's, I would want to be developing an animal model, which was actually based on noradrenergic transmission dysregulation.

So, if we look in our patient cohorts and we see that there are a sub-population of them who clearly have deficiencies in noradrenergic transmission according to the paradigms that we apply and that dysregulation is not associated with whether or not they have persistent pain, that’s telling us that there is a sub-population of patients whose Parkinson's is driven by dysfunction in the noradrenaline pathways. So, then we need an animal model to recapitulate that, and I'd be really interested in really looking at the brainstem A nuclei, which are the noradrenergic nuclei in the brain, and understanding how, if we disrupt transmission and signalling therein, do we then move towards developing a model that is akin to the Parkinson's patients where we're seeing a noradrenergic transmission dysfunction, and I think we've got so much more to learn from patient populations in that way of needing to back translate the mechanisms that we're just not doing yet. And that for me is something really quite important.

Evans

So you're looking at what is going on with people with Parkinson's and just working step by step backwards so that maybe with an animal model you can work out how to get from A to B?

Bannister

Yes. So the locus coeruleus which produces 95% of the central nervous systems noradrenaline has links to nuclei in the brain that govern reward and motor symptoms and sensory processing. And so that in itself provides quite a big clue that it's probably involved with aspects of motor and non-motor symptoms in Parkinson's. But none of the animal models that we have for Parkinson's recapitulate that. And this isn't true just for Parkinson's animal models. This is true for most of the models we're using. They're not faithfully recapitulating what is actually going on in the patient, and so it's no wonder that we don't have this amazing wealth of drugs coming out from animal studies because we've shown a mechanism and then we can apply that pharmacotherapy in the patient. We all recognise that there's not that translation and we need to ask ourselves why. And I think it's because we're not back translating enough information from the patient back to our animal, and then we're building a model based on that and that, I think, is an important direction that we should think about.

Evans

What animals do you use?

Bannister

So, *we* largely work with Sprague Dawley rats.

Evans

Right – this may be a daft question. How do you find a rat who has Parkinson's disease?

Bannister

Well you don't. You have to induce it. And that's the problem.

Evans

And to induce it you have to work out what's going on with the patient at the end of the thing. And that's why you need to go back and work out what the mechanisms are.

Bannister

Exactly. So, you know, lots of the models use lesioning techniques in those parts of the brain that really govern motor symptoms. And, as with the chronic pain models, that's the best we've had so far. But I think. as a field, we recognise that we can improve those and not just look at cellular markers. We actually want to understand the mechanism that we've observed in a patient cohort and now we're applying to an animal model and developing our animal models in a really different way and, like I say, that's true for *all* the models we're using, not just the Parkinson's model.

Evans

That's neuropharmacologist Kirsty Bannister, Associate Professor at King's College London.

Now, as in every edition of *Airing Pain*, I'd like to remind you of the small print, that whilst we in Pain Concern believe the information and opinions on *Airing Pain* are accurate and sound based on the best judgments available you should always consult your health professional on any matter relating to your health and well-being. They're the only people who know you and your circumstances, and therefore the appropriate action to take on your behalf.

It's important for us at Pain Concern to have your feedback on these podcasts so that we know that what we're doing is relevant and useful, and to know what we're doing well or maybe not so well. So do please leave your comments or ratings on whichever platform you're listening to this on or the Pain Concern website of course, which is painconcern.org.uk. That will help us develop and plan future editions of *Airing Pain*, but, to end *this* edition of *Airing Pain*, I want to return to the subject of spinal cord stimulators.

Earlier I was speaking to Professor Robert Brownstone as he was saying, for some it's changed lives for the better. For others, it's had limited or no effect.

So, what's the advice for someone contemplating the procedure? And where to get it from?

Brownstone

If they have what we would call focal pain – so the pain isn't all over their body – it might be worth discussing the pain in a Multidisciplinary Pain Clinic.

Some of the strongest evidence for the treatment of pain is a proper pain management programme, and so, even if people come to us, if they haven't done that type of programme, a self-management programme, they will do that before we get to them.

Evans

So that is what people should ask for first?

Brownstone

Absolutely. They're fantastic. A good pain management programme is worth its weight in gold.