

Airing Pain Programme 53: Headaches, chilli pepper patches, and the placebo effect

Investigating the diagnoses of headaches, and the benefits of topical and placebo treatments for chronic pain.

Paul Evans meets Dr Paul Davies, a Consultant Neurologist from Northampton General Hospital, who explains that whilst most headaches are benign and can be self-medicated, some headaches – those that are frequent and very painful – require medical attention. He outlines the different types of headaches, including migraines, tension headaches and cluster headaches, and says that each kind requires a specific treatment. Dr Davies admits that GPs have a long way to go in diagnosing and treating chronic headaches effectively.

Dr Mick Serpell, a consultant in anaesthesia and pain medicine in Glasgow, gives us an introduction to topical medicine – medication applied to the surface of the body rather than introduced into it. The medication is applied to the painful area and the drug has a painkilling effect at a local level. Topical medicines can take the form of a cream, a gel or a plaster impregnated with a drug. We hear about two types which are usually used to treat neuropathic conditions – lidocaine and a chilli pepper plaster. One benefit of topical treatments is that they have very few side-effects and can usually be used alongside other analgesics.

Finally, Paul meets Dr Michael Lee, a Research Associate at Oxford Centre for the Functional Magnetic Resonance Imaging of the Brain, who carries out extensive research into placebos – treatments given purely for psychological effect. In defiance of those sceptical of the placebo effect, Dr Lee's brain imaging research shows that placebo medications can have a visible effect on the way that pain is transmitted to the brain. Dr Lee also highlights the importance of psychological context in treatment, saying that what a patient believes about their doctor, their medication and the therapeutic process as a whole affects their response to medication.

Paul Evans: Hello and welcome to another edition of **Airing Pain**, a programme brought to you by Pain Concern. A UK based charity working to help support and inform people living with pain and health care professionals. This edition's been supported by a grant from the Scottish Government.

We all, I presume, get headaches. But when should we be seeking treatment from our GP? And will he or she be equipped with the right knowledge to help us? Doctor Paul Davis is a consultant neurologist at Northampton General Hospital. He also runs a headache clinic at the John Radcliffe Hospital in Oxford. He addressed health professionals at the Welsh Pain Society Annual Scientific Meeting on this very issue.

Dr. Paul Davis: The problem is that there are all sorts of different headaches, and some headaches are very serious and life threatening, but most of them are just very painful and we have many patients who are totally disabled with chronic headache. Although most

people have just intermittent problems which they may adequately treat with analgesics, but there is a proportion of headache sufferers that *really* do need medical attention that they don't always get.

Patients, when they first develop headache often think they have got something serious, but those are relatively rare and usually fairly easy to diagnose. The vast majority of headaches are benign and there are a variety of them, but the most common would be migraine which is a recurrent severe headache – it comes in various shapes and sizes. There's a tension type headache, which is just as common and again affects people with varying frequency and duration. And then there are some rarer but indeed very painful headaches, like cluster headache. This is a benign headache and it affects men more than women. It affects about one in a thousand people and it is often called "suicide headache" because it is so painful.

Evans: Are there problems with diagnosis?

Davis: Yes. The headache of course is just a symptom and we are trying to diagnose the cause of that symptom. There may not be a particular cause as such, like in migraine, or there may be a serious cause that you need to discover. But all headache diagnoses are firmly based on taking a good history from the patient; asking the patient about how long they have had the headaches, how often they occur, what they are like. And time spent taking the history will lead to a good idea as to the type of headache that patient has got.

The examination in most people will be normal, but of course in people with serious causes it may be vital to the diagnosis. Tests are often done but we seldom find results on tests like scans that we were not expecting, so the history is the key to the diagnosis.

Evans: So people who will be worried that they have got a brain tumour or anything, should they *really* be worried when they have a headache?

Davis: No. If headache is the only symptom, it is almost unheard of that they will end up having a brain tumour. Indeed, brain tumours tend not to give headache until they are really quite big, so they tend to present with people having seizures, or people having paralysis, or sensory problems. So really, it is pretty obvious when someone has got a brain tumour. They are so rare that in the vast majority of people you do not need any tests to prove that they do not have a brain tumour.

Evans: In your talk to the Welsh Pain Society, you talked about episodic headaches and chronic headaches. I presume an episodic headache is something that I or other people might have occasionally?

Davies: We take chronic headache to mean a headache that occurs on fifteen or more days in the month. In other words, it occurs most days: it may be all the time; it certainly must be most of the time. We need to diagnose the type of chronic headache, even though the patient may say, 'I have got a pain in my head every day'.

So there are several diagnoses where the pain is chronic: chronic migraine, chronic tension type headache, medication overuse headache, things like that. They are treated differently, so we must make a diagnosis even though they have got a pain all the time.

Evans: Do the same drugs that work for chronic pain work for chronic headache?

Davies: Not necessarily. Some do. So, for example, amitriptyline is used a lot in pain clinics for chronic pain; it is also used a lot as a migraine prevention pill, so it could be used for chronic migraine. Yet there are other drugs that are used a lot in chronic pain, chronic back pain, like pregabalin or gabapentin, which really are rather ineffective in the prevention of chronic migraine. So it is important to diagnose the type of chronic headache because it will influence the type of treatment you give patients.

Evans: It seems to me as a layman that there are different mechanisms working with chronic pain and chronic headache.

Davies: There must be a fair bit of overlap, but the fact that different drugs have different effects in these different pains and different headache syndromes does, I think, imply that there are different mechanisms. But I think also there are lots of similarities. If you have got a chronic migraine and it is different from a chronic pain in the head, it may still make you anxious or depressed and bring on a lot of those comorbidities that people who work in pain clinics see in patients with chronic back pain, for example.

Evans: Can we self-medicate our headaches?

Davies: Yes – and indeed most people do and for many people it is entirely safe and works satisfactorily so they do not need to seek medical help. I'm talking largely about the more benign end of the spectrum: people who maybe get migraine once a month or something like that.

The difficulty with self-medication comes if the headaches are very frequent. Then patients will want to take analgesics frequently or they may use them in the wrong way like, 'I'm going out tonight, I don't want a headache, I'll take two aspirin.'

And if they take analgesics too frequently, then they can lead to a disorder that has been increasingly recognised where the headache is a result of taking all this analgesia – medication overuse headache. There is no test for that and the only treatment is to withdraw the offending analgesics. And it is a huge problem.

Evans: What's your advice to people who suffer headaches?

Davies: It's important to have a diagnosis and often people know they have got migraine because the symptoms are so typical or maybe their mother had migraine and the mum says, 'Oh that's just a migraine.' But if they have troublesome headache and they don't know what is causing it, then they need to see a medical practitioner. They need a diagnosis so that they will receive the right treatment.

Evans: So are GPs particularly good at diagnosing headache?

Davies: Well, I think we know from studies that they are not particularly good. We know that if you have a headache and you go along to your general practitioner, the odds are you won't be diagnosed with your headache. As a result you will be given some analgesic, which, if it does not work, you will want something a bit stronger. And, you know, the last thing one wants to do is give strong analgesics to headache sufferers, as it just tends to make the problem worse. I think GPs are improving, but there is still a fair way to go in getting the right diagnosis.

Evans: Consultant neurologist Dr Paul Davies. I will just remind you that whilst we at 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. He or she is the only person who knows you and your circumstances and therefore the appropriate action to take on your behalf.

Now, a topical medicine is one that is applied to surface areas of the body as opposed to those which are delivered into the body, say by tablet or injection. They are an emerging area of interest for patients and physicians, so why is that? Dr Mick Serpell is a consultant in anaesthesia and pain medicine in Glasgow.

Dr Mick Serpell: I think it is important for us to distinguish what we mean by topical medicines. A lot of people will think, you know, a patch on the skin is a topical medicine and examples of that would be some of the opioid patches, you know, fentanyl or the buprenorphine patches, but also hormone replacement therapy and anti-sickness drugs – they can be given by patches. But they are tools that deliver drugs through the skin into the blood stream, so they are not topical. They are applied on the skin but they are working generally around the body by being absorbed into the blood.

Evans: So what does topical mean in this context?

Serpell: Topical means the medication is applied to the area that is painful and that predominately the drug is concentrated into that tissue and has an effect at that local level. Some of it will be absorbed into the blood but tiny amounts, and that won't be contributing to the pain relieving effect of the medication.

Evans: I am thinking now of people trying to give up smoking, if they put a nicotine patch on that goes into the bloodstream. But what we are talking about now is as if I have a pain in my leg I put a patch on there, and that just affects the pain on my leg, locally.

Serpell: That's right yes. So patch often means the drug is working, you know, systemically by being absorbed in the blood stream. It might be better to call all these topical therapies 'a plaster'. And, for example, the lidocaine plaster is something which works topically at the area that it is supplied to. Most people can associate the idea of a plaster, a bandage that you put on a sore bit, you know, a cut, and it is just over that local area. So 'a plaster' would be a better term because it is applied to the painful area and it works purely in that painful area. There may be overspill secondary benefits which we see with successful treatment but it is working predominantly at the local site of application.

Evans: Can you explain to me what these patches, or let's call them plasters if you like, what they are used for?

Serpell: Perhaps first it might be worthwhile just saying what topical therapy is, that most people may be more familiar with, that are out there in terms of pain killing treatments – and the anti-inflammatory gel, you can buy that from the chemists, that's just a cream, you rub that on a sore joint. And there is also the chilli pepper cream that has been out for 30-40 years – again that's a cream that you rub all over the painful area.

What's happened more recently is the development of plasters (as we are going to call them) which are a preformed material with the drug impregnated and you apply this to the

skin and the drug has its effect. The two main used ones are the lidocaine plaster, which has been out for over five years, and more recently the chilli pepper plaster. They are quite different drugs, they work in different ways and they work for different types of pain.

So the lidocaine plaster contains lidocaine which is a local anaesthetic that most people may be familiar with, getting from the dentists, a very old drug, about 60 years old. When it's concentrated into the plaster, and applied over the painful area it can have an analgesic benefit. It's used primarily for neuropathic pain conditions: that's nerve pain conditions. And, predominantly it's used for postherpetic neuralgia, but also sometimes diabetic neuropathy, but also postoperative wound, scar pains, if there is a neuropathic or nerve component to that. Some people have used it in some other conditions which it's not actually licensed for, but in palliative medicine, clinicians sometimes use it for, for example, bone metastatic pain deposits – it does have some benefit in some cases there.

Evans: Are there any down sides to using these medications?

Serpell: Well administering them topically has big advantages in general. Very little drug is absorbed into the blood stream. So therefore systemic side effects are much less common. But the drugs can have, you know, some minor effects. But, as a general rule, topical therapies have much lower side effects.

They predominantly have problems with local side effects, and that may be skin irritation, if the patient is allergic to the adhesive that is used to stick the plaster to the skin, or allergic to the actual ingredients, the drug ingredient. Some people are allergic to light local anaesthetics or to chilli pepper. But normally side effects are contained to the local tissues, so it's skin rash or redness. But there is a small number that do get systematic side effects of nausea, but you get that with any type of treatment, you know, placebo also has side effects like that. But they are much, much less than taking a systemic therapy.

Evans: Should you be aware of taking other pain killers, or other medicines when using these?

Serpell: Generally not because very little of the drug is taken into the blood stream so it should not really interfere or interact with other drugs that the patient may be on. And if you do get good effect, good pain relief by using a topical therapy that often allows you to reduce the dose and maybe even stop some of the drugs that you are taking for pain relief.

Evans: You mentioned chilli pepper. Now that's something that's used to induce pain, so how does it work as a pain relief?

Serpell: Yes, it's an interesting phenomenon. The actual proper name for the ingredient is 'capsicum' and when it is applied to the skin, you are quite right, it actually activates pain and certainly there are experimental pain models where you inject chilli pepper to induce an acute pain in order to sort of study it. So when you apply these creams or the chilli plaster patients often do get some pain. The more dilute creams, it tends to be more of a burning sensation; the stronger patch, which is about over 100 times stronger than the strongest cream, is quite a strong reaction: it can be actually painful during the application – but that will subside after a few hours or sometimes days.

But, you are quite right – what they do is stimulate the nervous system to begin with, so patients will get pain, and then it causes changes within the nerves, it's actually a neurotoxin, so it actually causes the nerves to, as it were, die at the peripheries and then retract into the skin. So there is some degradation. But this is reversible when the medication stops, the nerves will slowly grow back after a few weeks and the pain relief is induced by that mechanism.

Evans: So it's kicking the pain relief into action, basically?

Serpell: Yes. Nerve pain is induced by nerves that are acting abnormally, they are hyper excitable and throwing off electrical impulses which is continually giving the patient sensation of pain. The chilli pepper plaster will actually knock out the nerves and temporarily degrade them, so they are not functioning anymore and the pain settles down. But as the nerves regrow back – which all the evidence suggests at the moment that they grow back normally – then eventually pain most commonly returns again. And then a second application can be done and so on.

Evans: Do you become more immune to effects, the more you use?

Serpell: There is no evidence for that. Clinical trials are being done with patients getting repeat applications over a year and there is no evidence that you know, a third, fourth patch is any less effective than the first one. But as clinical experience, you know, accumulates as we have real patients who have actually have these plasters applied over several years, then we will get the true answer for that. But at the moment there is no suggestion that tolerance develops.

Evans: I take it that these aren't over-the-counter drugs?

Serpell: No. Both of them are prescription-only medicines. So in the first case, the lidocaine plaster your GP can prescribe them and the patient can apply them themselves. And usually with the lidocaine plaster it's put over the painful area for 12 hours and then taken off for 12, so it's a once a day or once a night application, but done every day.

The chilli pepper plaster is quite different. It's quite concentrated, quite potent, so the patient can't apply it to themselves. If you get it on your eyes, it can cause some serious damage. So it's actually applied by a trained individual, most commonly a nurse who has gone through a formal training process. And she will be wearing gloves at least, and often they have a mask on and eye protection and it is done in a well-ventilated room, because they do give off some fumes, chilli pepper fumes, and that can induce some coughing, airway irritation, sometimes runny eyes, if the concentration of vapour is too high. So that's why it is done in a proper setting, in a good well-ventilated room with a trained individual. And it's applied for one hour and then taken off.

A good responder will have pain relief lasting for three months or longer. So it's as it were a treatment that the patient will come in, get done and then they go away and they can forget about medication – hopefully forget about their pain, if they have had a good result – for many weeks, maybe months.

Evans: So who would be offered the chilli pepper patches?

Serpell: These would be patients who have neuropathic pain. It's licensed for postherpetic neuralgia pain. There are other nerve pains which it has been used for – it is also licensed for HIV-induced neuropathy and actually very few treatments work in HIV neuropathy, so this is the one of the few effective medications. So those two groups – HIV neuropathy and postherpetic neuralgia – but we know there are many other type of neuropathic pain patients out there and although clinical trials haven't been completed to warrant a granting of a licence indication, we as clinicians have used it in these off label conditions, like post-operative scar pain, and found good results in some patients. So I think the important thing is that patients get a proper assessment of their pain and are well informed of what their treatment options are. And drugs form a part of that treatment, but it's not the only part, and sometimes has very little, or sometimes even no role. I think it's important to look at the non-drug therapies, the physiotherapy, the psychology...

But if we're using drugs, we try and get a sensible combination of drugs that are going to be the most effective for the patient and have the least side effects. Particularly with resistant pain, you often have to combine drugs and maybe use two, three, four, sometimes five different drugs. So the more drugs you use, the more chance of side effects. So we are trying to sort of minimise that and one way of doing that would be the use of topical therapy where systemic side effects are, you know, generally much, much reduced.

Evans: Consultant in Anaesthesia and Pain Medicine, Dr Mick Serpell.

Well, what if the tablet you're taking could in terms of its chemical make-up have absolutely no side effects at all – indeed, no effect of any kind at all. In fact, unbeknown to you, you're only taking it because the doctor thinks the psychological benefits of taking it will far outweigh those of not taking it. The term 'placebo' – that pill or medicine given purely for psychological effects – actually comes from the Latin, 'I shall please'.

Michael Lee is a research associate at the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain. He's involved in extensive research into the so-called 'Placebo effect'. So is it correct to say that a placebo doesn't do anything?

Micheal Lee: It is, but there is a little bit more to that. The tablet itself is inert and as far as the patient knows, and maybe the prescriber knows, it's biologically inactive. And that's not the same as it doesn't do anything; clearly it does something, because you have what's called a 'placebo effect' or response, in that some patients do improve with this seemingly inert compound that they've just taken.

Evans: So do people actually give patients with pain conditions little white tablets that outwardly will not do anything to them?

Lee: If you are talking about current practice, then the answer is probably not. In fact, in a recent 2013 survey of GPs only 7 per cent would say that they have ever, ever prescribed a – what they call – a pure placebo, i.e.: a tablet that they know does absolutely nothing biologically. Most placebos are actually impure, so they have some action, but not necessarily for the condition that's being treated. So an example of that – and that's been of concern – would be prescribing antibiotics, which obviously have a biological effect, but for common cold which is a viral infection, because there is a strong belief by the patient, or perhaps by their GP, that this is going to be useful. But obviously this is not best practice. So that would be called an 'impure placebo'.

Evans: So that is purely to fool the patient?

Lee: Not purely to fool the patient, but perhaps to reassure. In fact, in the 1950s, placebo prescription was considered actually quite acceptable, in fact benevolent and kind. But that's really because we were at that time, in an era where we didn't have specific treatments for diseases, we only had very general panaceas.

Evans: With your study on placebo, are there actually any benefits?

Lee: Well, the thing about placebo is that it relies on the belief of the patient and also the interaction between a doctor and a patient as to how effective this tablet is going to be. Even if you take a tablet that is really quite effective you can always make it more effective by the way you present it, for example, its packaging, its cost and all that. So what brain imaging tries to do is to find out is this really related to a true pain-killing effect, or is it more related to what they call a report bias. So, if I treat you very well as a person, and I give you a tablet and even though the tablet isn't doing what you want it to do, but because I am really nice to you, you might come back to me to say, 'well Doctor Lee, I think it's really working.' Now for me that – you're better, but in reality you're not -- there's a report bias that's happening. So what brain imaging wants to do is capture objectively the actual brain response to pain that happens during placebo to see that there's an actual change in the way pain is being transmitted to the brain.

Evans: So can there be a response?

Lee: Absolutely, and that what brain imaging has shown, that in certain circumstances placebo has a very real response in terms of the way pain is being transmitted from the periphery to the brain.

Evans: How does that work, if there is no active ingredient?

Lee: It works really by the ways our brain has in terms of actually controlling pain. For example, you may in the heat of sports or vigorous exercise, you have not noticed being injured and therefore we have what's called an 'endogenous system' for control for pain, and this is the very same system that placebo utilizes. So our beliefs can actually activate this endogenous system and produce a very real effect in terms of pain transmission.

What we have shown in a brain imaging study of healthy volunteers given remifentanyl, which is a very powerful intravenous morphine – simply by telling them or making them believe that is going to work, or it's not going to work, and keeping a drop on all the time changes the way they perceive pain. So if they didn't think that the morphine is going to work, even though it was on, they just didn't get any benefit from it.

Evans: From personal experience – I have fibromyalgia, and I bought an electrical stimulation machine. When I bought it, it was absolutely fantastic [laughs]...like taking marijuana, and I said 'well, I have never taken marijuana, but if this is what it's like then, yes, it just relaxes me.' After three months I found that I hadn't plugged it in.

Lee: [laughs] Oh.... and what do you think about that?

Evans: Have I fooled myself? Does it matter? Because I was getting good relaxation out of it. In actual fact, since I have plugged it in it has been better, but now it hurts!

Lee: [Laughs] I think that just underlies how malleable the pain experiences are to, you know, what we believe of it and the treatment effects as well. You know, there is always something that

can be improved from biological treatments where it's just delivered, the best practice, and, you know, the psychological contexts are important. So, yes I would say continue to believe in the device. Like they say, you know, there are many things and the specific effects of treatment is quite small, and generally quite specific to the individual. But there's general incidental effects that what people call 'placebo' is just overwhelmingly quite important.

Evans: Michael Lee, of the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain. Before he has the last word, don't forget that you can still download all editions of ***Airing Pain*** from painconcern.org.uk. Or you can obtain CD copies direct from Pain Concern. Please do visit the website where you can find all sorts of essential information about pain management, including details of ***Pain Matters***, our magazine that compliments and expands on issues covered in ***Airing Pain***. As well as in paper form, ***Pain Matters*** is now available as a digital download and for those who use media on computers, tablets and smart phones the digital editions are not only a more convenient way of receiving your copy of ***Pain Matters***, but they offer an enhanced user experience with links to audio and other relevant information. So please do check it out at the Pain Concern website, and once again that's painconcern.org.uk.

The last word on the placebo effect:

Evans: If I have aches and pains, you're a doctor prescribing me a tablet, and I thought that was a tablet designed to help me, my brain would say, 'this is good.'

Lee: Absolutely. Yeah, what you believe about your medication is very important. Even if it has biological effects, you know, your interaction with a doctor, you are trusting him, your trusting the medicine and trusting the whole therapeutic process is very important. I can't emphasise how important it is to have a really good relationship with your prescriber. It's not just about the medicine: it's always more than that. In pain we always talk about the psychosocial model and even in prescribing in drugs that comes into play as well.

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