Special report

# Pain

Pain is one of the most integral parts of the human experience and our relationship with it is complex. We need pain for survival and yet it can drive us to utter despair. We experience pain as a physical process and yet the sensation of pain is created in the brain. What's more, this physical experience is deeply intertwined with our emotional state – indeed, emotional pain is a very real phenomenon. Perhaps it is no wonder that, even in the 21st century, our understanding of pain, what causes it and how to treat it is still far from complete. Improving our grasp of all this is crucial, however, as pain is on the rise and society's relationship with painkillers often does more harm than good. Thankfully, those studying pain are making some key breakthroughs on all these fronts, as we explore in the coming pages. Read on to discover what we now know about pain, to delve into the technological advances that can help understand and monitor it and to explore the prospects for new treatments to help manage the most prevalent health condition of our time.

## WHAT IS PAIN?

WHETHER it is a fleeting ouch from brushing against a hot oven or a longer-lasting throb from a broken leg, pain gives us an evolutionary imperative for survival. Without it, we might allow our tissues to be singed and battered without a thought. Life-saving it may be, but pain can also be catastrophically debilitating.

And it is a growing problem. Life expectancy is increasing, but those extra years are often associated with poorer health. Of all medical afflictions, the most common is pain, in particular chronic pain that lasts for more than three months (see "What is chronic pain?" page 42). We desperately lack effective treatments, and the ones we have bring their own problems, as evidenced by the opioid epidemic still ravaging the US, where the rate of opioid-related deaths increased by a third between 2020 and 2021. Pain is an increasingly challenging global health issue, hence the need for a better understanding of the experience, what causes it and how to treat it.

Remarkably, it is only relatively recently that we established a good picture of how and where the sensation of pain is created. On a basic level, this feeling is triggered in a similar way to all our sensory contact with the world around us. Receptors at the ends of sensory neurons collect information from the skin, muscles, organs, joints and any other parts of the body exposed to sensory stimuli, such as temperature, vibration and pressure. These neurons extend to clusters known as dorsal root ganglia, which shuttle signals to the spinal cord and brain.

When sensory stimuli are of a certain type and magnitude, they activate a receptor at the end of a particular type of neuron in these clusters, called a nociceptor, and the signals register as pain. This "painful" part of the process is known as nociception, the detection of noxious stimuli.

This basic mechanism for nociception has been known since the early 19th century, but the details have taken a longer time to pin down. It wasn't until 1997, for instance, that David Julius at the University of California, San Francisco, and his colleagues identified the gene *TRPV1* and the protein it encodes, TRPV1, which is found at the ends of nociceptors and makes cells sensitive to heat both from temperature and chillies. They did this by switching on genes that aren't usually active in cells that don't typically respond to capsaicin –

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> "The pain we experience isn't necessarily a reliable reflection of the threat it poses"

the chemical that makes chillies "hot". They discovered a single gene that made cells sensitive to capsaicin, as well as hot temperatures. For this work, Julius shared the 2021 Nobel prize in physiology or medicine with Ardem Patapoutian at Scripps Research in La Jolla, California, who discovered proteins that sense touch.

Identifying *TRPV1* filled in an important piece of the pain puzzle, as it offered hope of blocking the protein to treat pain. However, understanding – and ultimately blocking – the component of the pathway that shuttles the signal to the brain could provide more generic pain prevention. As it happens, this is already a rare but natural occurrence.

In 2006, Geoff Woods at the University of Cambridge and his colleagues reported on "congenital insensitivity to pain" (CIP), which is thought to affect just one in a million people. Those with the condition feel no pain whatsoever and, without the deterring caution it elicits, often don't survive far into adulthood. Some of the team had travelled to Pakistan to meet a boy with CIP, who attracted attention following incidents where he reportedly pierced himself with knives and walked on hot coals as street theatre. He died tragically following a jump from a rooftop before the researchers arrived. When the team studied DNA from the boy's extended family, including six other children with CIP, they discovered the root of the condition: a mutation in a gene called *SCN9A*, which provides instructions for making a sodium channel on nociceptors that makes them fire. Without it, pain signals never make it to the brain.

Is the next step a revolution in painkillers? If only it were that simple. For a start, blocking the routes used by pain signalling is prone to a plethora of hazardous and potentially fatal side effects (see "How can we treat pain?", page 44). What's more, we are increasingly understanding that nociception isn't the full story when it comes to the mechanism of pain.

The experience of pain is nuanced, involving a "pain network" – a multitude of brain areas with coordinated electrical activity. "We know that pain is highly complex," says Beth Darnall, a pain psychologist at Stanford University in California. "It's a noxious sensory experience, but it also includes emotional and social dimensions."

As well as nociception to tell us where it hurts, there is an affective, or emotional, system in the brain, which is even more complex and less well understood (see "What are the boundaries between emotions and pain?", page 40). "The context in which we experience pain, the meaning we attribute to it, our thoughts, our emotions, the quality of our sleep the night before – all of these things can have an influence on our experience of pain," says Darnall. So, the pain we experience isn't necessarily a reliable reflection of the threat it poses.

This link between quality of life and pain is a two-way street, and measuring things like sleep and mobility can give a window into the level of pain someone is experiencing and how to treat it (see "How can you measure someone's pain?", page 43). In fact, attempting to wrestle with a person's attitude to pain is one widely accepted non-pharmaceutical intervention, particularly for nociplastic pain (see "The third type of pain", page 41). Pain may be inevitable, but if understanding it better can diminish its impact, there is cause for hope.

**Stephani Sutherland**

## WHAT ARE THE BOUNDARIES BETWEEN EMOTIONS AND PAIN?

FEAR that makes you vomit, the sting of a rejection, paralysing grief – emotional pain can manifest in many physical symptoms. And while writers and musicians have spun tales and crafted songs intertwining physical and emotional pain for centuries, scientists have found it more difficult to describe the relationship between the two.

Now, recent breakthroughs are shedding light on the shared mechanisms that underlie both kinds of pain, offering an explanation as to why one leads to the other and providing avenues for treating some of our most debilitating conditions.

While senses like vision and hearing have nerve pathways that can be traced from the eyes and ears to a distinct brain region, brain activity in response to pain is more complex. It incorporates thoughts and emotions, which is why a good book can lessen a toothache, for instance, or the pain from a hot probe hurts more when you feel sad.

But emotions do more than just modulate existing pain symptoms. Distress from grief or embarrassment can lead to pain that may have no physical cause, but is no less real. Brain scans show similar activity in the pain network, which includes areas such as the insula, thalamus and anterior cingulate cortex that consistently respond to painful or attention-grabbing stimuli, when people are feeling psychological pain like social rejection and when they have physical pain.

Understanding the emotional aspects of pain could help tackle certain mental health conditions. Some studies have suggested that up to 75 per cent of people with chronic pain also experience anxiety and depression. "Having a predisposition for one of the conditions may make it more likely that you will experience another," says Felix Brandl at the Technical University of Munich, Germany.

To find out why, Brandl and his colleagues performed a meta-analysis of 320 brain scan studies of people with chronic pain, anxiety conditions and major depressive disorder. They found several shared brain changes, including similar decreases in brain volume and consistent changes in how neurons were connected in the prefrontal cortex – thought to be responsible for making judgements and goal-motivated actions – and the insula, which has been implicated in emotions, perceptions and self-awareness.

Brandl adds that psychotherapy and antidepressants have both been suggested to work on all three conditions. "Now, we have found overlapping [brain changes], we can better justify overlapping treatment strategies," he says.

Another potential explanation for the co-existence of chronic pain and certain emotional conditions is that they are both the result of chemical imbalances in the ventral pallidum, a brain region involved in our motivation to avoid pain and seek pleasure. Two chemicals are released here: glutamate and GABA, which lead to behaviour associated with fear and pain or reward, respectively.

Bo Li at Cold Spring Harbor Laboratory in New York suggests that conditions like chronic pain or depression result when the typical balance between these two chemicals shifts, producing a heightened sensitivity to potential threats that makes the individual more prone to pain and the urge to withdraw into themselves, while at the same time stifling the joy of reward. "This is a typical symptom of depression," says Li. "You aren't motivated to pursue otherwise meaningful things in life and are more sensitive to negative experiences."

### State of mind

While the emotional and physical side of pain are undoubtedly linked, in 2015, Choong-Wan Woo, then at the University of Colorado, Boulder, and his colleagues managed to distinguish for the first time between the neural activity associated with pain from a physical cause and that linked to state of mind. They did this by applying increasing heat to volunteers' arms during a brain scan. As the participants felt more pain, specific brain activity was triggered, which the researchers called the neurologic pain signature.

The experiment was then repeated, but this time the volunteers were asked to think of the pain as blistering heat or a warm blanket on a cool day, which let them alter the amount of pain they felt. As they did so, although the neurologic pain signature remained the same, a new brain signature appeared in a distinct set of brain structures. The team suggested that you could compare the strength of both types of signature to work out how much of a person's pain has a physical cause and how much is linked to their state of mind. Knowing this could help in conditions like chronic pain or fibromyalgia, the effects of which can be strongly influenced by emotions.

The relationship between physical and emotional pain is complex, but there is one clear benefit of overlapping brain mechanisms for both: you might have a treatment for some emotional pain in your cupboard. In 2011, researchers discovered that paracetamol (acetaminophen) not only helps reduce physical pain, but also blunts the pain of social rejection. To really underscore the importance of thoughts in tackling pain, it works best when combined with feelings of forgiveness towards those causing the pain.

**Helen Thomson**

"Paracetamol not only helps reduce physical pain, but also the pain of social rejection"

# THE THIRD TYPE OF PAIN

WE FIRST knew something strange was going on when Clare, my wife, was given intravenous morphine in the emergency room. She had excruciating pain in her ribcage and back, which had started months earlier and was getting worse. At its peak, she described it as feeling like somebody had thrust two swords between her ribs and was prising them apart.

Morphine gave no relief. The doctors were baffled. Clare spent five days undergoing tests. She was eventually discharged with a diagnosis of complex regional pain syndrome and a bag of powerful antidepressants, sleeping pills and anti-anxiety meds.

She didn't have complex regional pain syndrome. I looked it up and the pain was in the wrong place. But it took another six weeks to find out what she did have, during which time her physical and mental health declined alarmingly. I eventually secured a consultation with the complex pain team at University College Hospital in London, who told us she had nociplastic pain. It was a non-deteriorating condition, we learned, and it was manageable.

The team's leader, Fausto Morell-Ducos, explained that nociplastic pain is the "third category of pain". The first is nociceptive pain, which responds to an injury or inflammation. The second is neuropathic pain, caused by damage to sensory nerves. Both are created by the brain as a defence mechanism against further injury. The brain assesses signals from the damaged part of the body and transmits instructions back to the site of the damage that generate an appropriate level of pain.

Nociplastic pain is when that system goes wrong, a state known as central sensitisation. The brain's pain centre becomes hypervigilant and responds disproportionately to minor injuries or inflammation, converting them into excruciating pain. In some cases, there is no nociceptive pain at all, but the brain still sends out extreme pain signals. Negative mental states, such as anxiety or tiredness, can also be converted into pain. In Clare's case, the pain led to anxiety, which led to more pain, in a vicious cycle of torment.

Nociplastic pain was only added to the taxonomy of the International Association for the Study of Pain in 2017. There are several subcategories, including fibromyalgia and chronic primary musculoskeletal pain. The latter is what struck Clare.

Estimating prevalence is difficult as many people with nociplastic pain have one of the other categories of pain, too. But according to Mary-Ann Fitzcharles at McGill University in Montreal, Canada, it could be as much as 15 per cent of the general population, with women more likely to develop the condition.

Pain specialists believe there are two routes to nociplastic pain. One is bottom-up, where an "ordinary" pain trigger balloons beyond all proportion. Clare's started that way, with an injury. The other is top-down, where there is no obvious trigger. "In this context, we believe that the primary abnormality is centred in the nervous system," says Fitzcharles.

Doctors aren't widely aware of nociplastic pain and struggle to understand it, she says. "As physicians, we like to do a test that can direct us to a diagnosis. It's really challenging to see a person who looks completely well, the examination might be 100 per cent normal, but that person complains of a silent suffering."

## Limited options

Treatment options are limited. There is no magic bullet; no drug, surgery or talking therapy can quickly reverse it. Clare was prescribed antidepressants, which are the only category of drugs that the UK's National Institute for Health and Care Excellence (NICE) recommends. They helped, for a while.

"Management is very challenging," says Fitzcharles. The main focus of treatment is non-pharmacological interventions, such as mindfulness meditation or small bouts of activities that bring joy, designed to reprogram the pain-obsessed brain back to its default settings. NICE also recommends cognitive behavioural therapy and acupuncture.

Clare practised mindfulness and tried to find fragments of joy. She liked to be in nature, to go swimming and have foot massages. We did as much of those as she could bear, but these often led to flare-ups. When that happened, she was bedridden, in excruciating pain and ruminating on her predicament. The hole she found herself in became an abyss. She came to believe she was beyond help and attempted suicide three times. She finally completed it in August.

That is thankfully an unusual outcome – most people at least regain some quality of life, says Fitzcharles, though most will continue to endure some pain and have flare-ups. Up to 20 per cent of people with chronic pain conditions have suicidal thoughts, and 5 to 14 per cent go through with them.

It is too late for Clare, but there is hope. Neuroscientists are starting to understand how the neural circuits go awry. Pharma companies are working on drugs. "There's so much wonderful work going on, which will hopefully lead to new treatment strategies," says Fitzcharles. It cannot come too soon.

**Graham Lawton**

Need a listening ear? UK Samaritans: 116123 (samaritans.org). Visit bit.ly/SuicideHelplines for hotlines and websites for other countries.

## WHAT IS CHRONIC PAIN?

WHEN pain lasts for three months or longer, it is classified as chronic, a condition that affects more than 30 per cent of the world's population.

Chronic pain was long believed to be a stubborn version of acute pain – which passes in less than three months once the damage is healed – and it was treated in much the same way. Yet an increasing body of research has led doctors to believe that chronic pain should be treated as a disease in its own right, rather than an enduring symptom of tissue damage or physical trauma. This could have major implications for the treatment of lasting pain, together with the way we prescribe addictive opioids.

Recent research has revealed that in some people, chronic pain is a problem with the brain. An injury can lead to pain that persists after the tissue has recovered because the brain has rewired itself and learned to send pain signals, despite there no longer being a reason. Known as central sensitisation, it is as if the volume has been turned up on pain.

One way this seems to occur is when the brain experiences pain without relief for an extended period. "The brain interprets tissue damage and misfired pain signals exactly the same way," says Alan Gordon, director of the Pain Psychology Center in California. "[The pain is] all equally real and equally valid."

To help deal with the issue, Gordon has developed a talk therapy called Pain Reprocessing Therapy (PRT), which involves shifting people's beliefs about the causes and threat of pain (see "How do you treat pain?", page 44).

There are other explanations for chronic pain. In his book *The Song of Our Scars*, Haider Warraich at Brigham and Women's Hospital in Massachusetts, argues that chronic pain isn't always linked to physical sensations, but rather to a combination of physical sensation, emotional trauma and memory.

This fits with the fact that chronic pain can happen without any physical injury at all. Gordon describes people who come to him with chronic pain complaints without being able to identify any initial injury.

He believes chronic pain can occur when people experience psychological stressors as well as physical ones, which may be the result of an overactive fear response. "Somewhere along the way, their relationship with danger or fear has become oversensitive," says Gordon. This idea is supported by multiple studies showing an association between chronic pain and symptoms of post-traumatic stress disorder.

This oversensitisation of pain pathways is now implicated in many conditions, such as fibromyalgia, in which people experience widespread pain, often without a clear physiological cause – as well as chronic fatigue syndrome, irritable bowel syndrome and chronic daily headache.

The different mechanisms behind acute and chronic pain that research is beginning to reveal mean that for decades, people with chronic pain have been dismissed or wrongly treated by a medical profession that continues to prescribe therapies that work for acute pain, but, it transpires, simply don't work for persistent pain. Improved understanding of the distinctions now offer a more hopeful future with treatments that are non-addictive and work to target the real cause of the pain.

**Lucia Osborne-Crowley**

"The brain interprets tissue damage and misfired signals the same way"

## Painful prejudices

**It is a sorry fact: a woman's experience of pain is more likely to be dismissed than a man's. This "gender pain gap" is reflected in longer waiting times in emergency departments, a greater incidence of misdiagnosis of heart attacks and a lower likelihood of receiving treatment for pain at all. An exacerbating issue is the different mechanisms by which cisgender women and girls and transgender men experience pain through the activation of T cells – as opposed to the microglial cells activated in the spinal cord of cisgender men and boys and transgender women – which makes them more sensitive to painful stimuli. This has only come to light over the past 20 years because clinical studies were historically biased towards using male animals. Recent research also suggests transgender and cisgender women have a higher pain sensitivity compared with cisgender men, highlighting the importance of gender identity.**

**Other biases play into pain assessment too. Haider Warraich at Brigham and Women's Hospital in Massachusetts says someone's attractiveness, skin colour, language and socioeconomic status can all affect how and when pain is treated. "These all come to affect the person in pain, perhaps more than any other patient who seeks medical care," he says. He highlights a US study on appendicitis, a well-understood condition with straightforward tests and treatment, that involved were children. "My thought was we might have a kinder, gentler approach to children," says Warraich. Nevertheless, Black children were much less likely to receive opioids as a standard pain relief treatment compared with white children.**

# HOW CAN YOU MEASURE SOMEONE'S PAIN?

"PAIN yearns to be communicated," says Haider Warraich at Brigham and Women's Hospital, Massachusetts. Instinct makes us yell when we are hurt, and communicating pain is often described as a therapy itself – even screaming a swear word or two after stubbing your toe seems to soothe the agony. And yet modern medicine flounders when it comes to interpreting a person's pain. More often than not, it attempts to compress the physical and emotional complexity that contributes to the experience of pain into a single figure on a pain intensity rating.

That is problematic, says Jeffrey Mogil at McGill University in Canada, not least because rating your pain between 0 (none) and 10 (the worst imaginable) is intrinsically subjective.

One alternative is qualitative sensing testing, where you apply stimuli and ask the individual to indicate when they start to feel it, when it feels uncomfortable and when to stop. Mogil says this allows you to compare an individual's general experience of pain against the average, but says little about the pain that person is experiencing in the moment.

Another option is the McGill Pain Questionnaire. First published in 1975, it suggests 78 descriptors for pain, from "searing" to "annoying" and "blinding". A person chooses a number of words, each of which has an associated score that can be tallied. The individual also indicates the parts of the body experiencing pain and gives an intensity rating. Despite its subjectivity, Mogil says it is the intensity rating in the questionnaire that tends to get used the most.

Many researchers believe a more objective measure is needed. They are working on systems that go beyond self-reporting, attempting to find biological signals, such as pulse rates, sleep patterns or even brain activity, that could help to determine the type and intensity of a person's pain.

Progress has been made, says Irene Tracey, a neuroscientist at the University of Oxford. For instance, brain scans reveal a difference in the response to two painkillers – the opioid tramadol and pregabalin – which the person's own pain-rating scores don't reflect. You might wonder what good that is if the person taking the drug isn't feeling the benefit. But these insights are helping to piece together the extent to which different factors contribute to the experience of pain, all of which can point to different treatments, says Tracey, who described the experiment at the Advances in Pain conference in New York earlier this year.

For example, anxiety and depression can worsen a person's experience of pain, dull the efficacy of opioids and heighten the risk of chronic pain (see "What are the boundaries between emotions and pain?", page 40). The strength of social support networks and small variations in genes also feed into how a person feels and working out the best way to treat them. If a person's brain activity suggests they are responding well to a pain-relief drug, yet they are still feeling pain, it may be that one of the other elements is the predominant factor influencing their overall experience.

Artificial intelligence can also help by analysing multiple pain metrics. Tech and

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**A smartwatch helps monitor biometrics for gauging pain**

innovation firms IBM and Boston Scientific have embraced this approach with a joint project that began by recording 34 different metrics from 1700 individuals experiencing chronic pain. Pairing Boston Scientific's expertise in measurements with IBM's strength in machine learning, a team of researchers whittled these down to just seven types of useful data, which combine 12 of the original 34 metrics. Many of these can be recorded with a smartwatch and are a combination of self-reports on mood, alertness, sleep and so on, as well as objective measures, such as mobility.

The project uses AI to assess an individual's pain and predict how it will evolve, allowing personalised, pre-emptive interventions. To ›

demonstrate its effectiveness, researchers enrolled 76 people who were using spinal stimulators to manage chronic lower back or leg pain. For the first 30 days of the trial, participants followed their usual stimulation programme, which was based on standard recommendations. For the next 30 days, an AI analysed their metrics and gave daily recommendations for what stimulation programme to use. Participants recorded their pain intensity and the quantity of opioids used daily. At the end of the trial, 84 per cent of participants showed a significant improvement in pain experienced and quality of life with the AI recommendations.

For now, this approach still uses self-reported pain intensity scores in conjunction with biological measures. Ultimately, retaining an element of self-reporting may not be a bad thing, so long as the complexity of the pain experienced and its impact on quality of life is recognised. After all, "pain is subjective", says Warraich. "Subjective experiences are really at the heart of what makes us human."

**Anna Demming**

"Subjective experiences are really at the heart of what makes us human"

**An artwork memorialising people who died from opioid-related causes**

ALLISON BAILEY/NURPHOTO/SHUTTERSTOCK

## HOW DO YOU TREAT PAIN?

TENS of millions of people live with chronic and in some cases disabling daily pain in the US alone, in addition to those experiencing acute pain. Yet treatments for pain relief remain only partially effective and only work for some people.

For instance, paracetamol (acetaminophen) may have little or no effect on extreme pain and exceeding the recommended dose can be toxic to the liver. Similarly, ibuprofen and other non-steroidal anti-inflammatory drugs – which tackle the inflammation that presses on nerve endings and causes pain – have a range of side effects, including headaches and indigestion, as well as interacting with drugs used for several other conditions. This leaves opioids, which mimic the body's natural painkillers and are among the most effective form of pain relief.

Yet while opioids may work for many types of acute and chronic pain, they can be ineffective against others, and are associated with addiction and the risk of overdose. The opioid epidemic has cost hundreds of thousands of lives in the US and has underlined the need for alternative treatments. But as John Wood, a pain researcher at University College London, puts it: "There has been a tremendous succession of failures trying to make new analgesics."

For years, pharmaceutical companies had been looking for a way in through a single gene that might be vital for pain, he says. So, in 2006, when a team led by Geoff Woods at the University of Cambridge discovered such a gene, called *SCN9A* (see "What is pain?", page 38), "this seemed to be like manna from heaven", says Wood.

Sodium channels are a vital part of the process that allows neurons to fire. There are nine known types of sodium channel, each found in different parts of the nervous system and the heart. Blocking them all would be fatal, but *SCN9A* suggested a way to block pain signalling while leaving other sodium channel activity intact, because it encodes Nav1.7, a type of sodium channel found almost exclusively in sensory neurons.

However, while experiments had demonstrated that animals and people without *SCN9A* feel no pain, inhibiting Nav1.7 channels has rarely yielded the sought-after painkilling effects. Then, in 2015, Wood and his colleagues showed that the neurons scattered

throughout the body that release natural painkillers also differ in people and animals without Nav1.7 channels. This may explain why drugs that selectively block the channels fail to generate the full pain-blocking effect found in people who lack *SCN9A*. A more nuanced gene therapy approach is looking promising in rodent trials.

A surprising source of pain relief might be bacterial toxins. Researchers had previously attributed the pain of bacterial infection to the activation of immune cells causing inflammation, with the resulting swelling leading to pain. However, in 2013, immunologist Isaac Chiu and neurobiologist Clifford Woolf, both at Harvard University, and their colleagues found that bacteria could directly activate the sensory neurons that signal pain – as well as silence them.

The reasons for these effects aren't well understood. However, in 2021, Chiu led a study on mice with either acute or chronic pain and showed that toxins derived from *Bacillus anthracis*, the bacterium that causes anthrax, could silence sensory neurons. Crucially, the pain returned, indicating that the toxin hadn't damaged or destroyed the neurons, only temporarily blocked their activity. "This does show that microbes can be a source for therapeutics," says Chiu.

Yet chronic pain includes much more than a physical sensation – it is a complex emotional experience, too, and it should be treated as such, says Beth Darnall at Stanford University in California. She advocates embracing other methods, such as psychological treatments. "It's common practice to recommend such psychosocial strategies for pain only after all medications have failed, but our research is suggesting that we should apply this approach in all people, because a substantial subset benefit from it."

## Drug-free therapy

In a study of people undergoing surgery for breast cancer, for instance, those who participated in a programme of mindfulness, pain education and techniques to self-regulate pain called My Surgical Success needed opioid medication after surgery for five days less than a control group, without reporting higher pain.

In another study of a psychological treatment called Pain Reprocessing Therapy (PRT), which involves learning to reframe pain as non-threatening, 50 people were given four weeks of PRT and compared with groups given either a placebo therapy or routine care. At the end of the trial, 66 per cent of those in the PRT group were pain-free or nearly pain-free, compared with 20 per cent in the placebo group and 10 per cent of those who received usual care. Brain scans taken before and after the trial showed significantly reduced responses in pain pathways among people in the PRT group.

Darnall has developed her own programme called Empowered Relief, which consists of a single 2-hour session that is similar to My Surgical Success. According to a study of 263 people with chronic lower back pain, it can be as effective as eight 2-hour sessions of cognitive behavioural therapy, a well-established psychological treatment for pain, and it offers greater pain relief than a health education session that included information about nutrition and managing medications.

"We don't yet have very clear data on the mechanism," says Darnall, but she believes that these pain education programmes can help where opioids sometimes don't, because they equip people with a skill set to calm the nervous system, including pain and other stressors. "Medications alone don't do that," she says. ▮

**Stephani Sutherland**

## Placebo power

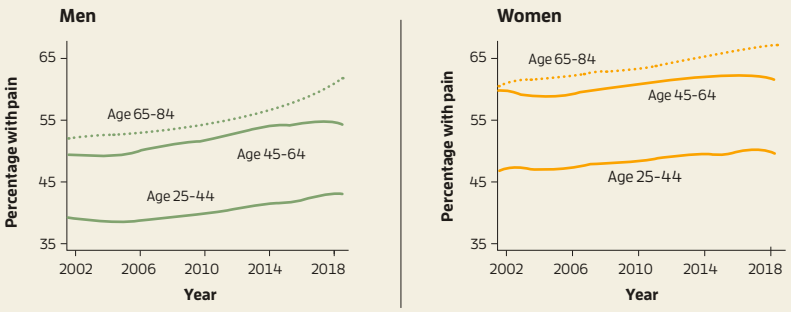
**A placebo describes a treatment that has no true medical effect, yet provides a benefit. According to Beth Darnall at Stanford University in California, pain's universality and malleability make it a useful paradigm to study placebo and nocebo, the opposite effect in which negative beliefs can worsen the pain experience. Researchers are trying to leverage the placebo effect to improve pain treatments.**

**"Placebo is really well studied in the context of pain," says Darnall. The effectiveness of placebos historically rests on deception: people experience a benefit because they have been told they were receiving an active treatment. But more recently, many studies have shown that "open placebos" – when people are explicitly told that a treatment is inert – can relieve pain as well.**

**Surprisingly, a study published in *Scientific Reports* in January suggests that placebos can work even when they aren't actually used. Participants who had possession of a placebo oil were able to withstand the pain of ice-cold water longer than those who didn't have the oil.**

### Pain prevalence

Trends during the period 2002 to 2018 for US adults aged 25 to 84 demonstrate the increasing prevalence of chronic pain, including lower back pain, neck pain, severe headache or migraine, facial or jaw ache and joint pain

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