DANIEL HERTZBERG

BIOMEDICINE

Move over, morphine

The dearth of treatment options for chronic pain has led to widespread over-prescription of strong opioids. But some innovative thinking is building a promising pipeline.

BY JAMES MITCHELL CROW

Michael was 15 when he was kicked in the back by another student at his school in Australia. The blow ruptured a disc in his lower spine, a painful injury that required surgery. In the weeks and months that followed, Michael had additional operations, but none were able to resolve his excruciating pain.

After 12 rounds of surgery — at the end of which, three-quarters of Michael's back had been fused with rods and screws — the pain was undimmed. Michael (not his real name) had spent most of his adolescence in hospital and had become morbidly obese.

"When I first met him at 20, he was essentially bed-bound, virtually no sleep from the pain, on crazy doses of strong opioids," says Marc Russo, who directs the Hunter Pain Clinic in Newcastle, Australia. "He was existing, but certainly not living."

Unfortunately, cases such as Michael's are not rare. Globally, around one in five adults — almost a billion people — has persistent pain, which is often accompanied by sleep loss, depression, unemployment and relationship breakdown.

And for most people, the pain does not start with a trauma, as it did for Michael, but rather with a small physical insult, says Lorimer Moseley, a chronic-pain researcher at the University of South Australia in Adelaide. "Maybe they bent over to pick something up and their back hurts." A bout of pain — whether it's back strain or post-surgical pain — is often short-lived. But for around 10% of these people, the pain does not go away; they have transitioned from acute to chronic pain.

As Michael found out, effective treatments are sorely lacking. "There are a range of options, and a lot of people don't respond to any of them," says Charles Brooker, a pain-management specialist at the Royal North Shore Hospital in Sydney, Australia. So acute was the shortage of effective drugs, that some doctors — particularly in the United States, but also in other Western countries, including Australia — began prescribing strong opioids for chronic pain.

That strategy has turned out to be tragically misguided, leading to an epidemic of opioid addiction. "Opioids almost never work in chronic pain, and cause untold misery," says pain specialist Andrew Moore at the University of Oxford, UK. The good news is that as researchers finally begin to understand the mechanisms of chronic pain, new therapies — both drugs and devices — promise a powerful set of alternatives to opioids.

FROM KILLING TO CAUSING PAIN

Opioids kill pain by targeting μ-opioid receptors on pain neurons in the spinal cord and brain. By binding to these receptors, opioids inhibit neurotransmitter release at the junction between pain neurons, blocking

the signal. "Strong opioids are wonderful for palliative care and acute pain," says Russo.

But for the long-term treatment of chronic pain, the side effects take a toll. The body quickly develops a tolerance, which doctors counter by escalating the dose. When Russo first began to see Michael for his back pain, one of his first interventions was to ease Michael off the opioids.

Understanding the mechanism of opioid tolerance may help researchers to find a way to avoid it. As more of the drug enters the body, non-neuronal cells known as glia take notice. Once thought to be nothing more than a scaffold for neurons, glia are now known to be active members of the central nervous system. One of the jobs of the glia is to keep watch for foreign invaders. High opioid doses seem to trigger a defensive response, causing the glia to release immune-signalling compounds called inflammatory cytokines, which stimulate the sensory neurons that the drugs are supposed to sooth. "The dose is so large it is now causing pain," Russo says.

But because μ-opioid receptors are such powerful targets for suppressing pain, research into new opioids has not been abandoned entirely. Researchers are looking for drugs that weakly activate the μ receptor, but also hit other targets, says Russo. Hitting the μ receptor disrupts the flow of pain signals to the brain. Ideally, dual-acting drugs would also activate inhibitory nerves that descend from the brain to suppress pain, he says. This is how two of the newer morphine-derived drugs, tramadol (approved in the United States in 1995) and tapentadol (approved in 2008), work.

James Zadina, a neuroscientist who studies novel opioids at Tulane University in New Orleans, Louisiana, has taken a different approach. "Instead of starting from the opium plant, we started from the brain," he says. The first big break came in 1997, when his team finally tracked down a peptide in the brain that binds to the μ receptor just as selectively as morphine does[1]. The compound, called endomorphin-1, is now recognized as the natural trigger of the μ receptor.

Endomorphin-1 elicited an analgesic response just as powerful as morphine, but without the side effects. "The old way of thinking was, any drug that hits that receptor is going to do pretty much the same thing," Zadina explains. In reality, however, drug molecules of different shapes can bind to the same receptor in different ways and trigger a different set of responses — a phenomenon known as biased agonism. In the case of the μ receptor, endomorphin-1 seems to selectively promote analgesia.

As drugs, natural endomorphins would be hopeless — they break down too rapidly in the bloodstream. Zadina and his colleagues have been testing endomorphin analogues with reinforced chemical structures. The hope is that these molecules will still trigger the same response as the parent compound. Zadina has identified four new analogues of endomorphin[2], and is now preparing to take the best-performing into clinical trials. That compound, dubbed analogue 4, provides "much longer duration of analgesia" than morphine, says Zadina. Tolerance is also reduced — and the compound does not seem to trigger the release of pain-stimulating cytokines.

"There are a range of options, and a lot of people don't respond to any of them."

In addition, analogue 4 does not seem to be addictive. The most compelling data, Zadina says, come from trials in which a rat can press a bar to self-administer the drug. A rat given access to morphine, he says, "will start pushing the bar like crazy. They don't do that for our compound."

CHRONIC-PAIN PROPHYLAXIS

However effective these pharmacological interventions prove to be, prevention will always be preferable. All chronic pain starts as acute pain. "It would be far better to extinguish it at origin," says Russo.

Several studies have pinpointed factors that predispose patients to chronic pain — susceptibilities that a simple questionnaire can flag. Pre-existing anxiety and depression put people at risk, as does pre-existing pain. "People with chronic migraine are more likely to get chronic knee pain after a knee operation," says Brooker. "Those people have a sensitized nervous system."

Multiple sensitization mechanisms could be at work. There is a simple test to see whether one particular gate in the pain pathway, called diffuse noxious inhibitory control (DNIC), is functioning. For most people, if you place their left hand in ice water, they don't feel mild pain induced by a laser shone on their right hand — the DNIC 'filter' in their spinal column is helping the brain to prioritize its response so that the person pays attention to the stimulus that is more likely to cause damage. "But 20% of people can still detect the pain on the right — which means they have an abnormal ability for pain signals to get through to the brain," Russo says. The DNIC filter is more likely to fail if a person is stressed, he adds.

A new type of spinal cord stimulation device is in clinical trials.

SALUDA MEDICAL

Another factor in whether a person develops chronic pain is the initial severity of the acute pain. The first 24 hours after a trauma or operation are thought to be crucial. "If your acute pain is very severe, your risk of chronic pain is much higher," says Moseley. "If we can reduce the activation of nerve cells that produce the danger message in the spinal cord, then we reduce the chance those nerve cells will sensitize and adapt." This provides a clue as to how to stop the nerve cells from firing after the injured tissue has healed.

Combine all these ideas, Moseley and Russo agree, and there's the possibility that doctors can intervene before chronic pain sets in. "If you come up positive on the risk-factor tests, a special rapid-response team will manage your pain in the first 24 hours," Russo says. These teams would use every pain-killing method at their disposal — from drugs to temporary nerve blocks — to make sure that the patient never rates their pain beyond mild on the pain scale, he adds.

Individuals at risk of developing chronic pain can also be offered targeted psychotherapy to help with the underlying issues that predispose them to it, and to educate them in the mechanisms of pain. In 2014, Toronto General Hospital in Canada became the first centre to implement such a comprehensive programme aimed at preventing chronic postsurgical pain. The team does not have randomized-controlled-trial data yet. But several hundred patients have taken part in the programme, and the results seem promising. "The data suggest we're doing something right," says Joel Katz, a pain researcher at the hospital.

NERVE ZAPPERS

For the patients that these early interventions don't catch — or the millions already living with chronic pain — there are other options in the pipeline, including one that is not a drug at all. Last year, Brooker carried out the first permanent implant of a smart electronic device that stimulates inhibitory neurons in the spine.

The main body of the device is a matchbox-sized titanium box housing all the electronics, which is placed in the fat layer just beneath the skin. A thin wire runs from the device to a metal electrode that is implanted next to the spinal cord.

Brooker's patient, Jaswir Grewal, had suffered debilitating back pain for decades. After the surgery, he said that the severity of his pain went from eight out of ten to about two or three with the flick of a switch.

CHILDBIRTH

Delivering more options for women

Most areas of medicine have changed radically since the 1940s. But women in labour have pretty much the same pain-relief options as their great grandmothers.

For generations, labour wards have offered a trio of escalating pain interventions: a mixture of oxygen and nitrous oxide (gas and air); an injection of the opioid pethidine, which can leave women feeling nauseated and 'out of it'; or an epidural anaesthetic that numbs the lower-body pain, but can restrict the woman to the bed.

But this could be about to change. Last year, midwifery researcher Julie Fleet (**pictured**) at the University of South Australia in Adelaide and her colleagues conducted a randomized clinical trial that compared pethidine with a nasal spray of the opioid fentanyl.

Fentanyl is not a new drug. But because the body clears it quickly, it was conventionally given through a drip, which restricts movement and limits its appeal on maternity wards.

Around a decade ago, a nasal version of the drug was developed for use by paramedics and on children's wards, where it is now used routinely. Fleet suspected that the reformulated drug could also make a difference in childbirth. The self-administered nasal formulation gives women effective pain relief and allows them to remain mobile during labour.

The researchers showed that although nasal fentanyl and pethidine both controlled pain equally, women who receive fentanyl had shorter labours, less difficulty establishing breastfeeding, and less sedation and nausea. More than 80% of women would use it again, compared with 44% for

pethidine[3], says Fleet. "They get the pain relief, but without the sedation, so could feel in control and be active in their labour."

The two hospitals involved in the trial now routinely offer nasal fentanyl to women in labour. Fleet is collecting data to assess whether women who take up this option are less likely to request an epidural.

"There is this big misconception that epidurals are very safe for the baby," Fleet says. "Epidural can be very effective, but it does have increased risks." An epidural is the only pain relief option that requires continual fetal monitoring, because it can cause the mother's blood pressure to drop, which reduces blood flow to the baby and increases the chance that a woman will need a caesarean or an assisted birth. "We think if we give them an option that's less invasive and still effective for pain, they won't need to go on to epidural." **J. M. C.**

Spinal cord stimulation was first trialled in 1967, but it has usually been a treatment of last resort. This is because the simple implants tend to move relative to the spinal cord as the patient moves — even when they breathe. The target nerve is therefore frequently under- or over-stimulated, and neighbouring nerves are hit, too. "You tend to pick up nerves to the ribs, which can be very painful," says Brooker. So people with the implant often turn it down, or even off.

"If your acute pain is very severe, your risk of chronic pain is much higher."

The device that Brooker implanted in Grewal is more sophisticated. Created by start-up company Saluda Medical in Artarmon, Australia, the device overcomes the problem of electrode movement by continually reading the electrical activity induced in the target nerve, and adjusting its output to keep nerve stimulation within the therapeutic range.

Saluda had already demonstrated the concept's potential using temporary implants, and in October 2015 the company began a multinational three-year clinical trial of permanent devices — which Grewal was part of. While this is taking place, the company is continuing to improve the device, including miniaturizing it. "Making it half as big is not out of the question," says senior vice-president Dan Brounstein.

The Saluda device has impressed pain researchers. "In theory, it's a very significant development," says Russo, whose pain clinic is participating in the trial. It used to be impossible to know how much of the time the correct level of activation was being delivered to the target nerve. "With this device, it's close to 100% of the time," says Russo.

A wave of similar technologies may be on the way, thanks to an explosion of innovations in spinal cord stimulation. Among the ideas being tested are whether the use of high-frequency electrical impulse patterns suppress pain more effectively, and the use of inductive coupling (the technology behind wireless mobile-phone charging) to power the implant — so that the mobile-phone-sized battery can be worn on the belt rather than implanted under the skin alongside the stimulation device. "It is far more comfortable," says Russo, adding that implanting the device "becomes an outpatient operation".

As the technology has improved, so has the clinical knowledge of which patients will benefit. Those with neuropathic pain from damaged nerves respond the best. "For many years, we were able to achieve 50% of patients achieving 50% pain reduction," Russo says. In the past 4 years, several clinical studies have got close to 75% of patients achieving 75% pain relief. "Once you get to those figures, it no longer makes sense to be a treatment of last resort."

The developments in medication and technology have been welcomed by Michael, who is now 28. He has a spinal implant, and is taking a tailored cocktail of drugs. Together, these therapies have reduced his pain significantly, allowing him to sleep. He has lost 30 kilograms and is mobile, independent, has overseas holidays and an active circle of friends. "Yes he still has pain," Russo says. "But he is living life."

It might be an age-old phenomenon (see page S18), but pain, says Russo, was only established as a medical speciality after the Second World War. "We are the youngest field of medicine," he says, "and changing probably faster than any other."

The fast-blowing winds of change carry the promise of new drugs, devices and early interventions, which many pain clinicians hope will soon translate into better pain-relief options for their patients (see 'Delivering more options for women'). "It's like everything has been thrown up in the air and we're waiting for the dust to settle," says Brooker. "We're waiting to see which of these new toys really is effective once the clinical research is complete." ■

CATHY KEMPSTER

James Mitchell Crow *is a freelance science writer based in Melbourne, Australia.*

1. Zadina, J. E., Hackler, L., Ge, L.-J. & Kastin, A. J. *Nature* **386,** 499–502 (1997).
2. Zadina, J. E. *et al. Neuropharmacology* **105,** 215–227 (2016).
3. Fleet, J., Belan, I., Jones, M. J., Ullah, S. & Cyna, A. M. *BJOG* **122,** 983–992 (2015).