Delivery from discomfort

Pain is the dominant symptom in sickle-cell disease, yet it is poorly understood — and people with the disease face both medical and socioeconomic challenges in seeking effective relief. **By Bianca Nogrady**

ILANA PANICH-LINSMAN/NYT/EYEVINE

A person with sickle-cell disease with intensifying back pain receives a blood transfusion.

"Dealing with pain is messy," says John Roberts, an oncologist at the Yale School of Medicine in New Haven, Connecticut. It can't be measured objectively through biomarkers or visualized on a scan, the experience of it varies enormously from person to person, and it can be fiendishly difficult to treat.

When it comes to the chronic pain of sickle-cell disease, it gets even messier. Chronic sickle-cell pain can completely immobilize one person, whereas another is able to continue with their day-to-day activities. A dose of opioids that all but eliminates pain in one person can worsen it in another. Medical marijuana can help, not because it relieves the pain but because it helps people to be less bothered by it.

New disease-modifying treatments (see pages S2 and S8) are currently applied too late in life to prevent the accumulated, and so far irreversible, damage thought to be responsible for the constant background pain that is the physiological 'soundtrack' to life with sickle-cell disease.

When Roberts began treating people with sickle-cell disease, it soon became clear what the dominant issue was. "The most common reason why sickle-cell patients seek care is for pain," he says. Roberts was involved in a study[1] that found that a majority of adults with sickle-cell pain reported significant pain on more than half of the days covered by the survey. "People who had been listening to their patients had known that for decades, but it had never been documented in the medical literature," Robert says.

The pain of sickle-cell disease is multidimensional: it presents as both acute episodes of intense pain and chronic background pain. The two forms seem to have different causes and might require different treatment approaches, although both are poorly understood.

Acute pain is often sudden, and typically drives people to the emergency department. It's thought to be caused by sickled red blood cells blocking small blood vessels, leading to a loss of oxygen to the surrounding tissues, causing damage and tissue death. It also involves the release of a cascade of inflammatory molecules and cells that themselves cause nerve pain. Disease-modifying treatments aim to prevent these 'vaso-occlusive crises' and, by extension, the acute pain that accompanies them.

Chronic pain, however, occurs even in the absence of vaso-occlusive crises. It does not necessarily correlate with disease severity, and disease-modifying treatments don't lessen it[2]. This kind of pain is poorly dealt with across many conditions, but in sickle-cell disease it presents an especially intractable problem for researchers, clinicians and patients. The underlying physiology is not yet well understood, although research suggests the pathophysiological mechanisms are different from those underlying the acute pain in sickle-cell disease. Inflammation and damage to tissues, bones and nerves are accompanied by an increased sensitivity to touch and desensitization to drugs that might relieve the pain.

The most commonly used treatments are opioids. Even when these drugs work, they come with a host of problems, including addiction, side effects such as constipation, nausea and itchiness, and the risk of overdose — all of which are made more likely because some people experience such severe chronic pain that they require massive doses of opioids simply to function.

And because sickle-cell disease predominantly affects those of African, Middle Eastern and Indian descent, people with the disease who live in countries such as the United States must also grapple with systemic racism that means their symptoms are sometimes not taken seriously, or are even dismissed as a ploy to get narcotics. Lack of privilege can also impede access to alternative and non-pharmacological treatments that could offer some relief. In lower-income countries, treatment options are even more limited and difficult to access.

Despite the many roadblocks that people with sickle-cell disease face in achieving relief from chronic pain, the simple recognition of the unique nature of their pain means there is finally an incentive to better understand and treat it. Hope lies in a multidisciplinary approach, bringing together haematologists,

neuroscientists, psychologists, biochemists and alternative-medicine practitioners.

Cascading into crises

The vaso-occlusive crisis has long been the focus of researchers working on treatment, says Amanda Brandow, a paediatric haematologist at Children's Wisconsin hospital in Milwaukee. "In my mind, that's a very different thing than interventions that treat the terminal clinical symptom, which is pain," she says. Much of the research effort has focused on disease-modifying therapies, but by the time a patient has started receiving them, the damage thought to be responsible for chronic pain has already started to accumulate. If disease-modifying therapies could be given at an early age – perhaps at one or two years – that might prevent the damage from inflammation, vaso-occlusion and other disease effects from accumulating, and therefore potentially prevent the chronic pain, Brandow suggests. But until that damage can be prevented from the very beginning of life, Brandow says, more research is needed to understand chronic pain.

Research into the neurobiology of sickle-cell pain is revealing that the damage caused by vaso-occlusive crises marks the start of a cascade of physiological changes, mediated by inflammation, that alter the nervous system permanently. "The understanding of how that inflammation has crosstalk with the nervous system, I think, is something that we're just beginning to uncover," Brandow says.

Kalpna Guta has been studying the mechanisms of pain in sickle-cell disease for decades. She says that in the landscape of chronic pain, sickle-cell pain is different. "We all know about chronic pain because it occurs in lower-back pain, it occurs in cancer, it occurs in diabetic neuropathy, chemotherapy-induced neuropathy," says Gupta, a haematologist at the Center for the Study of Cannabis at the University of California, Irvine. But in sickle-cell disease, the chronic pain is incredibly complex.

Research in animals and people suggests the chronic pain is neuropathic – it results from damage to the nerves. The vaso-occlusive crises are one likely cause of that damage, Gupta says, but outside those crises, the oxidative stress, inflammation and ruptured red blood cells associated with sickle-cell disease could also cause injury to neurons. For example, her research suggests that mast cells – which play a role in inflammation and allergy, and are activated during a vaso-occlusive crisis – could be interacting with nerve fibres and causing pain even after the crisis has passed[3].

Another important mechanism in chronic sickle-cell pain might be central sensitization, which is when the central nervous system gets over-stimulated and becomes hypersensitive, capable of interpreting even typically non-painful stimuli as pain.

Research into chronic pain in sickle-cell disease is further complicated because the best available animal models – mice engineered to develop the disease – do not perfectly mimic disease in humans. "Mouse to the patient seems like it's missing a step in the middle," Brandow says. This is driving researchers to use human tissue to try to create a more accurate picture of neurons in sickle-cell disease.

The opioid conundrum

Looking across the treatment landscape for pain in sickle-cell disease, one group of drugs dominates: opioids. That's not ideal. "The best drugs we have are opioids, and opioids are double-edged swords," Roberts says. Despite being the most effective pain treatment available for sickle-cell disease, they come with numerous problems, both medical and non-medical.

Against the backdrop of the opioid crisis – an epidemic of opioid overuse and misuse affecting the United States in particular – managing opioid use in people with both acute and chronic sickle-cell pain is difficult. "The typical dilemma that an emergency-room doctor faces," Roberts says, "is am I treating this patient with opioid because they're having pain and I'm going make the pain better, or are they pulling the wool over my eyes and they're really just drug-seeking?" This is especially problematic given the high doses of opioids that many people with sickle-cell disease need to manage their pain. There have also been concerns about individuals developing a tolerance for opioids, which means they require higher and higher doses to achieve the same level of pain relief. In some cases, opioids can actually make people more sensitive to pain – a phenomenon called opioid hyperalgesia[4].

All of this means clinicians need to have a thorough understanding of the nature of patients' pain, how they are coping, what their health-care-seeking behaviour is like, and how they use medication generally. One individual might only turn up to the emergency department when their pain is unmanageable and a dose of opioids that would "put you and me and another room of people asleep" will only take the edge off it, Roberts says. Another might neglect their regular health-care appointments but will turn up at the emergency department several times a day seeking opioids. And yet another might use opioids as a general-purpose chemical coping mechanism that also helps them manage insomnia and depression.

Furthermore, most people with sickle-cell disease in the United States are Black, and that brings another complicating factor, Brandow says. "The racial inequality of disease is intertwined with pain and our patients sometimes not being believed that they have pain," she says. "Oftentimes you have no visible physical exam findings or tests that you can do to prove the patient does or does not have chronic pain, and I think that's always a challenge for our patients when they try to seek care for their chronic pain."

DAVID DERMER/AP/SHUTTERSTOCK

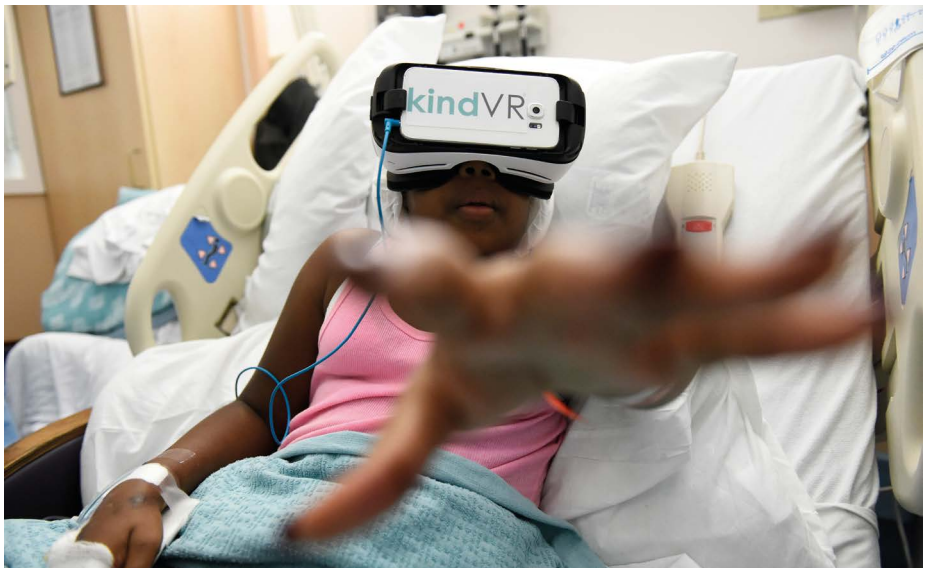
Medical marijuana can help to manage pain.

Just being able to access opioids can be an issue in some countries, such as Nigeria. "Opioids are very strictly regulated – you cannot get those in the hospital," says Obiageli Nnodu, a haematologist at the University of Abuja. She says that people being treated for chronic pain "are supposed to have oral morphine, but it's not that widely available and you certainly can't get it over the counter".

There are concerns that the use of high doses of opioids in people with sickle-cell disease could be associated with reduced lifespans, as Gupta and colleagues have found in some studies of people taking opioids for cancer pain. But it is difficult to study whether some people with sickle-cell disease have an opioid dependency or whether those high doses are genuinely helping to manage their pain, because it would be unethical to take them off the only thing treating their pain.

Gupta and colleagues' study in sickle-cell mice suggests that fears about dependency and mortality might be unfounded[5]. They found that sickle-cell mice that were treated with opioids survived longer than those that weren't. The study also suggested that the mice did in fact need increasing doses of opioids to manage their pain: this was not a function of addiction or tolerance.

"The physicians who are compassionate, they say this is what they see in the patients also, that when they are not on morphine and



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Virtual-reality technology is used to help distract children with sickle cell from their pain.

they've been on morphine, their pain intensity is much higher," Gupta says.

Cannabis and beyond

Although opioids might be effective at managing pain, the problems associated with their use are driving interest in both pharmacological and non-pharmacological alternatives to help people with sickle-cell disease manage chronic pain.

In Nigeria, the main drug used is pentazocine. It is not strictly an opioid, even though it interacts with the opioid receptors, but is nonetheless associated with misuse, says Nnodu, with people self-injecting and developing hard-to-treat ulcers as a result. Clinicians also use diclofenac – a non-steroidal anti-inflammatory drug – and paracetamol combined with codeine, as well as the opioid tramadol.

Elsewhere, antidepressants such as selective serotonin reuptake inhibitors are also used to help manage chronic pain[6].

One drug of increasing interest is cannabis. In the United States, around one-third of people with sickle-cell disease have used medicinal cannabis daily, mainly for pain relief[7]. Its use is associated with decreased use of painkillers[7] and fewer hospital admissions[8]. However, the story of cannabis for sickle-cell pain is complicated.

The first issue is that there are two main psychoactive ingredients in cannabis: tetrahydrocannabinol and cannabidiol. The first is responsible for the 'high' of marijuana, but the second is the one of medical interest because it is thought to be responsible for clinical benefits, including control of nausea and vomiting. But too high a dose of either ingredient can have unpleasant effects, so the challenge is to find a way to achieve the analgesic effects without making people insensible, which can be difficult to achieve when buying medical marijuana on the open market in states where people with sickle-cell disease don't have access to prescription cannabis products.

> **"The best drugs we have are opioids, and opioids are double-edged swords."**

Even when the dosage is carefully controlled, it's still not clear just how, or even if, cannabis helps. Gupta and her colleagues ran a clinical trial in which people with sickle-cell disease underwent a hospital stay, during which they were randomized either to cannabis administered by a vaping device or a 'placebo cannabis' three times a day for five days. The patients were then swapped onto the other arm of the study, with a period of two months in between, so they acted as their own control.

Unfortunately, the study wasn't able to recruit enough participants, which meant that even though there was evidence of a decrease in pain when they were treated with cannabis, it was not statistically significant. However, the treatment was associated with a significant decrease in the impact that pain had on mood[9].

Despite the lack of a statistically significant direct effect on pain levels, Gupta says the findings were encouraging. "This clearly shows that we need to expand studies like this, with a very well designed clinical trial where we can really have multiple comparisons," she says.

There is also growing interest in non-pharmacological interventions to help people with sickle-cell disease manage their pain. The 2020 American Hematological Society guidelines for management of acute and chronic sickle-cell pain[10] cautiously recommended cognitive behavioural therapy – a form of psychotherapy – on the basis of evidence for its effectiveness in other chronic-pain conditions such as fibromyalgia and lower-back pain. The guidelines also suggested acupuncture and massage therapy, although the authors acknowledged that there was limited evidence for their effectiveness in chronic sickle-cell pain.

But leaving aside the question of effectiveness, there are problems with access to non-pharmacological interventions, and they are often not covered by health insurance. In Nigeria, such interventions are even more challenging for people with sickle-cell disease to access, says Nnodu, although those with chronic pain who are struggling with dependency on pain medications can be referred to a hospital psychologist or psychiatrist for treatment. However, the absence of publicly funded health care means these treatments are available only to those who can afford them.

The landscape might seem grim, but Gupta is optimistic that treatment of chronic pain in sickle-cell disease is on the cusp of major advances, in both drug development and more-holistic management.

"We have enough evidence of many targets at the moment, which are disease-modifying in a way that targeting them would prevent chronic pain," she says. "But we also have enough evidence to improve analgesic strategies – the combinations and with integrative approaches."

But to achieve this, medical science needs to take pain as seriously as the underlying disease – something Gupta says hasn't yet happened in clinical research. "We care more about the disease, and then pain," she says. "We cannot just cure one and not the other: they are absolutely interdependent."

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