Recent advances in the management of chronic pain

KATE STEWART

Current treatments for chronic pain are often ineffective and are associated with some problematic side-effects. This article discusses some new approaches that may offer better treatment options for patients with chronic pain in the future.

Every day, millions of patients across the UK make an appointment to see their GP because they are in pain.

For some people, it is acute, severe pain caused by an injury or a disease such as cancer, which can be highly effectively treated with a wide range of opioids like morphine and tramadol. For others, where the pain is less severe, a weaker opioid such as codeine can be prescribed. Common side-effects of opioids include sedation, dizziness, nausea, vomiting, constipation, tolerance, respiratory depression, physical dependence and addiction. These are clinical concerns that may prevent proper prescribing and in turn lead to inadequate pain management.

For patients with chronic pain, suffered by nearly 10 million people in the UK almost daily, according to the British Pain Society, non-opioid drugs such as paracetamol and NSAIDs, including aspirin, ibuprofen and diclofenac, are often prescribed. But for many, these painkillers have little or no impact and some experts claim they can actually make the patient’s pain worse. In addition, NSAIDs can cause side-effects, including indigestion, stomach aches, nausea and diarrhoea, as well as stomach ulcers that can lead to internal bleeding and anaemia.

New pharmacological treatments

So what hope is there for GPs and prescribers that new, improved pain-relieving drugs and treatments will soon become available to improve patients’ quality of life, particularly for those with long-term pain?

Leading neuroscientist Professor Stephen McMahon is Sherrington professor of physiology at King’s College London and director of the London Pain Consortium. He works on new analgesic drug development and is very optimistic that there will be new classes of analgesic drugs in the future. “It’s all very good news, something I could never have said 10 years ago, as there has been a dearth of new products,” he tells Prescriber.

He continues: “There are several new treatments in the pipeline; some are
“NGF inhibitors work in the clinic; the only issues are the side-effects and bringing them to market. They are monoclonal antibodies so they won’t be cheap – there are several practical problems, but this is likely to be a completely new class of drug in the armoury of physicians before too long.” One downside is that the therapy will need to be injected, but antibodies persist in the body for many weeks. “Tanezumab is usually dosed every eight weeks, and experience with other monoclonal antibody treatments suggests that nurse- or self-administration is well tolerated,” adds Professor McMahon.

He continues: “Another class of compounds, which are orally available small molecules that block P2X3 receptors, a type of purinoceptor found on nociceptors (pain-sensing neurones), have now been tested in a few phase 2 and phase 3 trials and show a lot of efficacy in chronic cough.2 One drug in this class has been extensively tested in the clinic and is definitely effective for cough, so it’s going to be developed and tested out for a range of related conditions. It doesn’t have a licence yet but has good phase 2 and 3 data – so it’s quite likely to be available as the first of a completely novel class of drugs to treat pain-related problems.”

Another hope on the horizon is a new class of angiotensin II-receptor antagonists that targets type 2 receptors (the current angiotensin II-receptor antagonists licensed for the treatment of hypertension and heart failure target type 1 receptors) for the treatment of neuropathic pain.3 The first drug in this class has shown some efficacy in diabetic neuropathy and is now being investigated in a larger range of clinical conditions, notes Professor McMahon.

“And the one that the whole industry is really waiting for but it’s a bit frustrating because it hasn’t panned out yet, is a blocker of Na1.7 sodium channels, which play an important role in the activation of nociceptors. Genetic data has shown that if you can find the right drug that’s very selective for Na1.7 it’s likely to be a very good analgesic, which if developed could lead to the complete abolition of pain of different kinds,” says Professor McMahon.

He continues: “So, many drug companies have been looking at ways of blocking Na1.7. There have been a few failures and modest successes, and even though it hasn’t quite been cracked yet, in terms of promise, all the evidence suggests that this is going to be a great target if a drug can be developed.”

Nonpharmacological treatments
Professor McMahon adds that lots of drug companies are also developing electronic devices to deliver pain relief that are being trialled extensively. These so-called ‘electroceuticals’ are not drugs but devices that deliver electrical stimulation, often at very high frequencies, to different parts of the body as a therapy. Techniques such as epidural stimulation and vagal nerve stimulation, which can be quite invasive and expensive, are being developed for chronic pain.

Professor McMahon has “mixed feelings” about this development because he believes the evidence base is much weaker than for drug trials. “You often
More distant therapies

Consultant in pain medicine at Royal Liverpool University Hospital and a council member of the British Pain Society, Dr Austin Leach remarks: “There are plenty of reasons to be optimistic that pain will be better managed in the future. I believe that over the next 20–40 years there will be more potential arising from epigenetics, the study of the way our genes can be switched on and off, and neuroplasticity – the process that allows the neurones in the brain and spinal cord to compensate for injury and disease, and to adjust their activities in response to new situations or to changes in their environment.

“Epigenetics is having a huge impact on breast cancer treatments – making it much easier to target treatment individually by looking at which genes are active and which genes are dormant in any particular patient.

“We are hopeful that this approach can be replicated in other body systems. So I suspect that in the future, we will be able to target drugs or drug combinations that are more effective – because if a person has x gene then drug A will be better than drug B for their pain. It could be years before we can achieve this level of sophistication but we are inching towards a target and as we do so, the treatments are getting better.”

A combined approach to pain management

Dr Leach points out: “Opiates are still very useful drugs – it’s their extended use for long-term pain that is being increasingly questioned. Currently we accept that opioids are not without their problems, but with careful management they remain extremely valuable drugs and they cannot be completely discarded, as thousands of people do benefit from taking them.

“For some people, their only strategy is taking tablets. I have no doubt that a combination of approaches that may incorporate the use of drugs is a much more effective way of managing long-term pain. This includes psychological treatments, relaxation and realism – accepting you have a medical problem and looking at ways to manage your life better around it, rather than hoping for an impossible cure. Healthcare professionals can provide much of this support through the pain clinic.”

Consultant in pain medicine at Southmead Hospital, Bristol, Dr Cathy Stannard comments: “I don’t think we’ll get more effective drugs for treating pain but I do think we are getting wiser about where medicine fits in pain management.

“Drugs can sometimes make a patient’s quality of life worse because of side-effects and what people often need to do with long-term pain is learn how to manage it. There are patients that need to be taken off medication that is not managing their symptoms effectively.

“There is no painkiller that has no side-effects, even paracetamol has more side-effects than we first thought,” Dr Stannard adds.

“For long-term pain, anxiety and distress make a large contribution to how you feel your pain. So molecules that block pain signalling from the periphery are never really going to cut it because the process is much more complicated and we need to recognise that.

“A very central message that people find quite difficult is that actually being able to target drugs or drug combinations is an impossible cure. Healthcare professionals can provide much of this support through the pain clinic.”

Dr Stannard continues: “GPs have told me they don’t feel they are addressing the patient’s needs because they never get the chance to sit down and hear their full story. I have more time than GPs and so I can give the patient an hour to get the full picture of which medications are helping and worth taking and which ones are not. This helps the patient feel heard and understood.

“Some of the patients that I see end up being harmed by doctors because they are given medicines that don’t work, they end up having investigations that they don’t need and eventually someone might even operate on them.” She adds: “We need to help prescribers not make those kind of emotional decisions and be more analytical – is this drug going to help and if not, we should not prescribe it,” she warns.

Dr Stannard continues: “GPs have told me they don’t feel they are addressing the patient’s needs because they never get the chance to sit down and hear their full story. I have more time than GPs and so I can give the patient an hour to get the full picture of which medications are helping and worth taking and which ones are not. This helps the patient feel heard and understood.

“Some of the patients that I see end up being harmed by doctors because they are given medicines that don’t work, they end up having investigations that they don’t need and eventually someone might even operate on them.” She adds: “We need to help prescribers not make those kind of emotional decisions and be more analytical – is this drug going to help and if not, we should not prescribe it,” she warns.

Resources

For more information, including tips on how to manage pain, visit Arthritis Research UK’s website at: www.arthritisresearchuk.org

To find out more about treating patients with arthritis, there is a free ‘Core skills in musculoskeletal care’ programme. Visit www.arthritisresearchuk.org/coreskills.aspx

Arthritis Research UK has also put together a self-management information guide for living with long-term pain. The guide has information about different approaches to pain relief and who to ask for support. Visit: http://www.arthritisresearchuk.org/arthritis-information/arthritis-and-daily-life/pain-and-arthritis/pain-report.aspx

Visit www.paincommunitycentre.org, a learning resource developed by Cardiff University for health professionals seeking evidence-based information and education on pain and its management. It includes pain toolkits for headache, fibromyalgia, rheumatological conditions, neuropathic pain and many other conditions.
the pain enough so that you can get on and do things.”

Dr Stannard suggests that GPs can empower their patients to manage chronic pain by highlighting the importance of maintaining mobility, exercise, general fitness and general health. “Helping patients improve their sleep will also improve mood and pain. Also, making sure that if people do have depression, it’s managed on its own merit, as that will help their pain,” she adds.

Dr Stannard notes that some people will get benefits from a raft of different drugs and they should be offered them and closely monitored. “Pain is difficult to treat – but not because we have not got the right drug,” she adds.

Natalie Carter, head of research liaison at Arthritis Research UK, says: “Pain is a huge problem for people with musculoskeletal conditions but they are very unhappy with what is currently on offer because either they fear the side-effects or the painkillers are not very effective, especially for people with conditions like fibromyalgia.

“We don’t think there is anywhere near enough investment in pain research at the moment, and we are aiming to rectify that with a planned £5 million investment this year. We fund a centre of excellence at the University of Nottingham, which is specifically focused on pain. The researchers there are looking at whether painkillers already developed for other diseases can be repurposed and used in arthritis, and osteoarthritis specifically.

“We believe there will ultimately be pharmaceutical solutions that will provide a painkiller for people with arthritis and chronic pain that works for them,” she concludes.

References

Declaration of interests
None to declare

Kate Stewart is a freelance health journalist

POEMs

Meta-analysis: alpha-blockers effective for kidney stones

Clinical question:
In patients with kidney stones (ureteric calculi), is treatment with an alpha-blocker effective in improving passage rate and decreasing pain?

Bottom line:
Although a recent large study found no benefit to alpha-blocker treatment (Lancet 2015;386:341–9), this meta-analysis of 55 studies found a benefit to using alpha-blockers to increase the likelihood of stone passage, decrease surgical intervention, and decrease episodes of pain. These findings support European and US guidelines that recommend their use. Patients with larger (at least 5mm) stones are more likely to benefit. (LOE=1a)

Reference:

Study design: Randomised controlled trial (single-blinded).
Funding source: Self-funded or unfunded.
Allocation: Concealed.
Setting: Population-based.

Synopsis
To conduct this study, the authors searched five databases (including Cochrane CENTRAL), a previous systematic review, reference lists of other reviews, and clinical trial registries. Two researchers independently selected randomised controlled trials that compared alpha-blockers with placebo or no treatment in patients with ureteric stones. Two researchers independently extracted the data from 55 studies enrolling a total of 5990 patients.

Stone passage, which occurs in approximately half of patients without intervention, is 50% greater with treatment (number needed to treat [NNT] = 3.74) and will occur an average 9.5 days after presentation as compared with 13.3 days without treatment. Episodes of pain will also be decreased. The need for surgery will decrease by approximately half (NNT=6.17) and hospital admissions will decrease approximately 60% (NNT=10.6) Patients with larger stones (at least 5mm) are more likely to benefit. There was some evidence of publication bias; for some outcomes, results were calculated only using data from the larger studies. There was significant heterogeneity among the studies regarding stone passage rate.