Pain is an important issue for both society and health care. With recent news showing effectiveness of gene silencing in the prevention of pain transmission, combined with people living longer with increased comorbidities and the unresolved US and potential UK current opioid crises, the development of novel and effective pain treatments will surely throw the matter of pain relief into even starker light.

Across Europe, an estimated 100 million people have chronic pain, while the number is more than 50 million adults in the USA and estimates in the UK are at approximately one in seven of the population. These high numbers are complicated by the variety of causative conditions and the variance in pain severity, frequency, and onset. Individuals living with chronic pain can have huge disruptions to their ability to work and enjoy a healthy quality of life. In the USA, the annual burden on society has been estimated at $560–635 billion. The increasing frequency of individuals with chronic pain as the result of chronic diseases and postoperative pain have directly led, over the past two decades, to the over prescription and misuse of opioids.

What is referred to as the opioid crisis describes both the medical overuse and subsequent addiction by patients to opioid prescription and synthetic drugs. Opioid side-effects include poor coordination, mood swings, depression, and anxiety combined with a dependence on the drugs. The damage to an individual can affect all facets of day-to-day life with the increased risk of fatal overdose. Although the crisis is firmly established in the USA, reports of a 400% increase in opioid prescription over the past decade and an increase in deaths from fentanyl from eight to 135 per year in the UK suggest this problem is not limited to North America.

Opioids are a diverse family of painkillers, which include fentanyl, oxycodone, codeine, hydrocodone, and other compounds. In the late 1990s, the addictive qualities of these drugs were underestimated, leading to their widespread prescriptive use as post-surgical and chronic pain analgesics. In early 2019, an estimated 130 people per day were dying from opioid-related drug overdoses, 2 million people were misusing first-time opioid prescriptions, and almost 33 000 deaths were attributed to overdosing with synthetic non-methadone opioids in the USA alone.

In recognition of this epidemic, governments and health-care organisations have used a wide range of approaches to counteract the increase in addiction and addiction-related deaths. In 2012, the US Food and Drug Administration (FDA) developed a risk evaluation and mitigation strategy for all health-care professionals, using extended-release and long-acting opioid analgesics. This programme sought to educate health-care professionals on proper prescribing practices via training and distribution of learning materials. The US Department of Health and Human Sciences (HHS) implemented a five-point strategy in 2017, detailing a need for better data, prevention strategies, pain management, reversing drugs, and research. Concerns exist, however, as to the effectiveness of either the FDA or HHS’s initiatives and indeed how the direct effects of these initiatives can be assessed are still unclear. The holistic approach to combat the opioid crisis especially involves the next generation of caregivers. Medical students are trained to be more conscious on this matter, given specific training not just on appropriate prescribing procedure, but also on an individual’s opioid use sourced from non-official health-care outlets.

The question remains, why are we still using opioids as a health-care modality? Part of the complex reason is the striking efficacy of these molecules as analgesics in comparison to alternative therapies. One approach to address this issue might be the development of novel pain treatment modalities reproducing the highly effective activity of opioids without the addictive and lethal side-effects. In the wake of the opioid crisis, research efforts have turned towards a number of pharmaceutical solutions to this issue.

The combination of existing analgesics with better targeting offers another avenue for future pain treatments. A 2018 study by Maria Maiarù and colleagues at University College London (London, UK) published in *Science Translational Medicine* investigated targeting opioid receptor positive cells using the effects of the toxin botulinum. The researchers created a molecule dermophin, which targets opioid receptors, is subsequently taken into the neurones and can prevent neurotransmitter release, preventing pain signal transmission. In mouse models, dermophin shows a long-lasting painkiller effect and, most importantly, without the long-term addictive effects of a true opioid.

Conotoxins, produced by sea snails are a potential alternative therapy for pain, which have fewer side-effects and much decreased addictive properties than opioids. Ziconotide is a synthetic conotoxin currently available for use, with the main drawback being the decrease in effectiveness when delivered via a mode other than cerebrospinal infusion. Other synthetic conotoxins, which might be delivered by more facile methods are currently under development.

Glia cells are another potential target for new pain-reliving drugs. A number of the molecules designed to target glial cells show complementary activities with opioids. Ibudilast is a molecule that acts on the inflammatory cytokine interleukin 1 beta. The direct effect of ibudilast is a protective role during morphine-induced hippocampal injury. An added effect is to enhance oxycodone efficacy. As a result, ibudilast is of interest as both an enhancer of the safety profile and efficacy of opioids. Although not a new drug, minocycline has shown the capability to attenuate morphine tolerance and enhance morphine efficacy. Development of similar molecules could provide improved pathways to treat individuals in the midst of opioid addiction.
Gene therapy continues to promise much for a number of diseases. Studies to date have focused on the gene SCN9A in the treatment of chemotherapy-associated pain. For cancer patients, a high dose of chemotherapy can offer better chances of survival, but also increased chronic pain. Increases in chronic pain can often prompt patients to discontinue chemotherapy, because such treatments for pain with fewer deleterious effects would play an important role in cancer treatment. Using animal models and epigenomic editing, Jinping Shao and colleagues at Zhengzhou University (Zhengzhou, China) showed in a study published in *Molecular Pain* that silencing of SCN9A alleviates pain sensitivity transmitted via the spinal cord. If reproduced in human trials, this kind of treatment would be highly effective in decreasing chemotherapy-related opioid dependence.

Concerningly, over the course of the last decade, a sizable number of new opioid drugs have received US FDA approval. Dsuvia, an opioid formulation designed for use by military personnel, controversially received US FDA approval in 2018. This new formulation is five to ten times more potent than fentanyl. With the approval of other new opioids, it is becoming clear that the pharmaceutical industry, even in the shadow of the current epidemic, is not finished with this family of drugs. Without coordinated and cooperative effort between health-care advocates, government policymakers and politicians this crisis cannot be resolved. The research community should receive more support to develop novel and safer pain therapeutics, aiding society’s ability to move away from these dangerous, addictive drugs. Without taking a hold of this crisis on all levels, there is no doubt that we will continue to see this crisis extended globally.