

The opioid crisis and ... reconsidering the use of drugs that affect body temperature

The New York Times recently reported that opioids are now the leading cause of death of Americans under the age of 50 [1]. This shocking statistic is a current assessment of the deadly effects of opioids due primarily to respiratory depression in what has now become known as the “opioid epidemic”.

Opioids comprise a family of medications that have universally acknowledged efficacy for acute moderate-to-severe pain and for cancer pain. Their use in chronic, non-malignant pain, however, has been controversial both in terms of uncertainty of long-term analgesic benefit to patients and concerns about whether they improve quality of life in such patients. Physicians have become increasingly aware of the dangers of opioids, but treatment of chronic pain remains one of the greatest clinical challenges of our age. Based on a 2011 estimate by the Institute of Medicine, 100 million people in the United States suffer from moderate to severe chronic pain, and nearly 10% of our populations suffer from such pain each and every day with a national annual economic cost of \$560-635 billion.¹ These estimates reveal the limitations of currently available therapeutics that are often unable to provide adequate relief of pain. Even in patients experiencing benefits from opioids prescribed for pain, these drugs produce severe side effects such as somnolence and mental clouding, hyperalgesia, tolerance, addiction liability, physical dependence, constipation, urinary retention, as well as hormonal dysregulation, all of which dramatically reduce quality of life. In spite of these drawbacks on patients and the risks to society, physicians often do not have other pharmacological choices to achieve adequate pain relief in some patients. The need for discovery and development of pain-relieving drugs that can provide therapeutic benefit to patients without the danger of overdose deaths, addiction and dependence is now more urgent than ever.

The NIH Office of Pain Policy recently announced the release of the Federal Pain Research Strategy that emphasized research priorities that are intended to help fill crucial gaps in the federal pain research portfolio. The “development of safer opioids, new, non-opioid analgesics and the first generation of disease-modifying agents” has been identified as a “top priority” of the Federal Pain Research Strategy. In June and July 2017, the NIH hosted three meetings focused on creating public-private partnerships to address the urgent public health need associated with opioids [2]. The NIH joined with the National Academy of Medicine and with private partners in the pharmaceutical industry and the research community to launch an opioid research initiative with the goal of cutting in half the amount of time required to develop: 1) safe, more effective strategies for pain management; 2) new and innovative opioid addiction treatments; and 3) overdose reversal interventions. Among the workshop objectives was the goal of “considering the formulation of promising pain medications—beyond opioid analgesics—that may have been shelved by companies” [3].

The search for non-opioid mechanisms for treatment of pain has been ongoing for many decades. An important breakthrough occurred in the late 1990s with the identification of the molecular sensor of noxious heat, a cation channel that is referred to as the TRPV1 channel (Transient Receptor Potential cation channel subfamily V member 1), a member of a broad family of channels that are transducers of sensory stimuli. The TRPV1 channel is now known to be the transducer for noxious heat and can also be activated by acidic conditions (as commonly associated with injuries) and chemicals (such as capsaicin, the extract of hot chili peppers). Importantly, the TRPV1 channel is found on primary afferent nociceptors, and its activation produces sensations of pain in humans. The discovery of the TRPV1 channel led to a massive effort on the part of the pharmaceutical industry to develop antagonists of this channel as novel non-opioid analgesics. Studies soon showed that blocking the channel was also associated with potential negative outcomes. As might have been anticipated, blocking a heat sensor resulted in the inability of humans to detect noxious heat, impairing a critical physiological, protective role of pain. Additionally, blockade of TRPV1 was shown to lead to hyperthermia, a potentially dangerous effect

that inhibited further development of this class of compounds (for a review, see [ref. 4](#)). More recent evidence reveals that, in some cases, TRPV1 blockade also produced hypothermia [4]. The clinical question of whether blocking TRPV1 could produce analgesic benefit for patients was thus never fully answered.

The opioid epidemic has yet another side. Millions of surgeries are performed annually in the United States and around the world. As population growth accelerates, and as our citizens age, the numbers of surgeries performed will undoubtedly increase further. An often underappreciated factor in opioid dependence and addiction is persistent opioid use after surgical procedures in a vulnerable population. A recent study published in *JAMA Surgery* demonstrated that incidence of new persistent opioid use (continued opioid use beyond 3 months post-surgery) is as high as 5–6% [5]. These patients were opioid-naïve prior to the surgery, and, interestingly, the persistence of opioid use was independent of the initial severity of the surgery. Thus, each year, millions of opioid-naïve patients are at risk of becoming opioid-dependent.

During surgery, patients often exhibit a significant decrease in core body temperature (i.e., hypothermia) while under anesthesia. Anesthesia-induced hypothermia is associated with a number of significant health-related problems, including increased surgical site infection, increased bleeding, poor wound healing and overall slower recovery with longer hospital stays and increased pain. These complications result in an economic impact of millions of dollars in healthcare costs, as well as loss of work hours and increased suffering for patients, further impacting the healthcare system. Anesthesia-induced hypothermia is currently managed by physical means involving attempts to warm the patient with forced-air warming blankets or with infusions of warm fluids. However, these means can be inadequate in many larger surgeries and can be associated with their own complications such as risk of burn injury. Currently, no pharmacological treatment exists for anesthesia-induced hypothermia.

We recently proposed to use the hyperthermic effect, a major side effect of many TRPV1 antagonists, to counteract anesthesia-induced hypothermia [6]. We demonstrated that TRPV1 antagonists may be repurposed to prevent or treat surgical anesthesia-induced hypothermia, while also reducing post-surgery opioid requirements in rodents [6]. We also paved a way of how to convert this idea and our preclinical findings into a drug [7]. The potential use of TRPV1 antagonists to treat this important problem not only will be the first pharmacological approach, but it may have important implications for reducing opioid use in the post-surgery period and thus helping to limit the extent of the opioid epidemic.

There are potentially other ways of utilizing various properties of TRPV1 antagonists for drug development. For example, those compounds that do not affect body temperature (i.e., cause neither hyperthermia nor hypothermia) can continue being evaluated as potential analgesics, and several pharmaceutical companies are working in this direction. A more speculative application would be to repurpose the hypothermia-inducing TRPV1 antagonists for the induction of therapeutic hypothermia, perhaps to replace TRPV1 agonists, which have been proposed for this purpose [8]. As in the case of using the hyperthermic effect of TRPV1 antagonists to counteract the hypothermic action of anesthesia, using their hypothermic effect in therapeutic hypothermia may come with added benefits of analgesia and reduction of opioid use. All these proposed uses are consistent with the Federal Pain Research Strategy and the goals of the NIH to reconsider “shelved non-opioid analgesics”, including TRPV1 antagonists—compounds that are widely known to affect body temperature.

Note

1. Due to the strict limit to the number of references, we cite some statistics and widely known facts related to the use of opioids without supporting them with proper references.

References

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