

Special Section on The Opioid Crisis

Editorial

Translating Pharmacology into Therapeutics to Fight the Opioid Crisis

The opioid crisis challenges the health care system in North America. Overdose deaths due to opioid use were estimated to reach 47,600 in 2017 (Scholl et al., 2019); more than the number of deaths due to gun violence. In addition to this frighteningly high number of overdose deaths, over 2 million Americans have been diagnosed with opioid use disorder (OUD), stressing the medical system with other challenges such as neonatal abstinence syndrome and the spread of infections such as human immunodeficiency virus and hepatitis C. The escalating opioid crisis is a perfect storm due to multiple factors. These factors include opioid misuse and diversion, opioid addiction, inadequate penetration of medications for the treatment of OUD, the acute influx of especially potent μ -opioid receptor agonists such as fentanyl and carfentanil, and the stigma surrounding OUD and its treatment. In a national response to this urgent health crisis, Congress has appropriated \$500,000,000 to the trans-National Institutes of Health (NIH) initiative called the NIH Helping to End Addiction Long-Term InitiativeSM. The two primary objectives of the NIH Helping to End Addiction Long-Term InitiativeSM include: 1) enhancing pain management, including developing nonaddictive pain treatments and advancing understanding of the biologic underpinnings of chronic pain; and 2) improving prevention and treatment of opioid misuse, OUD, and overdose (Collins et al., 2018). This present issue is focused on research and reviews relevant to the scientific foundation necessary to address the opioid crisis.

An excellent overview of this entire area is provided by the article “The Opioid Crisis and the Future of Addiction and Pain Therapeutics” by Nathan Coussens et al. This article provides highlights of a 2-day meeting hosted by the NIH on February 7–8, 2019, in Bethesda, MD. A valuable link is provided in the article, allowing readers to view the presentations from the academic, industry, and government representatives. A critical issue is the need to optimize the education of the healthcare workforce to mitigate the current opioid crisis and prevent future escalation. Authored by Brian Cox, Thomas Cote, and Irwin Lucki, the focus of the article “Addressing the Opioid Crisis: Medical Student Instruction in Opiate Drug Pharmacology and Pain Management” is to train future physicians in best practices for minimizing opioid misuse and diversion as well as identifying and managing acute/chronic pain conditions and OUD.

Several articles address different OUD treatment strategies and overviews of opioid withdrawal and overdose. A vaccination approach to prevent/attenuate fentanyl-induced overdoses is described by MD Raleigh and colleagues from the University of Minnesota, while preliminary clinical data with a small molecule approach using intranasal nalmefene is described by Philip Krieter and colleagues from NIDA and Opiant Pharmaceuticals. David Maguire and colleagues describe preclinical data for a new chemical entity, OREX-1019, developed with the goal of producing potentially beneficial effects for both the treatment of OUD and relapse prevention by reprising promising clinical data of combining buprenorphine with naltrexone. Kelly Dunn and colleagues draw on both preclinical and clinical evidence to provide a review of the nonopioid neurotransmitter systems that may contribute to opioid withdrawal syndrome. Randy Torralva and Aaron Janowsky from the Oregon Health and Science University explore how noradrenergic mechanisms may play a role in fentanyl-mediated rapid death, potentially explaining a component of the shortcomings of naloxone in this acute clinical emergency.

Additional articles address the issue of optimizing pain management as one of the critical pathways leading to OUD and potential opioid overdose. Max McDermott and colleagues from Utah State University and Mount Sinai describe how a recently deorphanized receptor, GPR171, may regulate morphine antinociception. James Meyer et al. from Amgen describe extensive work following an observation that sepiapterin reductase inhibition might attenuate tactile paw withdrawal responses. While these studies did not confirm the hypothesis, the rigor with which they were carried out is exemplary and an important facet in rapidly deciding whether to pursue novel targets/pathways into the clinic. Shane Kaski and colleagues determined that the functionally selective κ -opioid receptor agonist nalfurafine enhanced

morphine-elicited antinociception, but not its proaddictive properties. Thus, the G-protein-biased agonist nalfurafine might be beneficial as an opioid-sparing adjunct to enhance the antinociceptive properties of μ -opioid receptor targeting medications. Another contribution by Fernando Barreto de Moura et al. from McLean Hospital/Harvard demonstrates that nicotine enhances opioid nociception in primate models.

This collection of original articles and reviews emphasizes the need for an orchestrated effort of preclinical and clinical research to successfully arrest the opioid crisis and address the strains upon both healthcare delivery systems. Most importantly, the research advances reported here offer hope to afflicted patients and their families, who too often have suffered the tragic grief of prematurely losing a loved one. This effort, as addressed by the Helping to End Addiction Long-Term InitiativeSM, emphasizes that new scientific understanding and treatment directions are required to treat the manifestations of opioid addiction and overdose. The same is true in the development of novel nonopioid analgesic compounds. In addition to hitting the right molecular target(s), there is an urgent need to make sure that clinical trials are conducted and interpreted with necessary rigor to detect the true positives and not prematurely discard candidates that might be false negatives due to inadequate assumptions about the clinical population, to tune sensitivity toward signal versus noise, and to determine changes in the effect size of standard of care treatments for relatively mature clinical indications (e.g., most chronic pain indications).

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References

- Collins FS, Koroshetz WJ, and Volkow ND (2018) Helping to end addiction over the long-term: the research plan for the NIH HEAL initiative. *JAMA* **320**:129–130.
Scholl L, Seth P, Kariisa M, Wilson N, and Baldwin G (2019) Drug and opioid-involved overdose deaths—United States, 2013–2017. *MMWR Morb Mortal Wkly Rep* **67**: 1419–1427.

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