Hijacking the endogenous opioid system to treat pain: who thought it would be so complicated?

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In this issue, there is an especially interesting and important special review by Ballantyne and Sullivan entitled, “The discovery of endogenous opioid systems: what it has meant for the clinician’s understanding of pain and its treatment.” This review adds to these authors’ significant prior contributions to the pain field, as they are now proposing that many of the problems associated with opioid therapy can be understood mechanistically as being off-target effects on the endogenous opioid system. They describe how our emerging understanding of the endogenous opioid system might allow us to better understand how exogenous opioids can “hijack” this system to produce unexpected and undesired consequences, both when they are used for pain relief, and when they are misused or abused. They especially focus on how acute or chronic opioid therapy (COT) may impair some of the nonanalgesic functions of the endogenous opioid system, including on stress, mood, reward, and social bonding. The review also highlights a growing literature on how endogenous opioidergic tone may impact opioid system responsiveness in various acute and chronic pain states. The authors do not attempt to delve deeply into opioid neuroscience—but instead purposefully cover a wide number of topics somewhat superficially to help post biological mechanisms that may underlie some of the observed clinical phenomenon of opioid treatment.

This review is very topical because while the United States struggles with an opioid epidemic that is, killing tens of thousands of individuals in the general population with addiction and overdose, we in the chronic pain field have somewhat different but equally vexing problems with opioids. Yes, our patients with chronic pain are also dying of opioid overdoses. All-cause mortality is substantially higher in patients with chronic pain on opioids than in those patients with chronic pain not on opioids (who also have higher all-cause mortality), and some but not all of this excess mortality is certainly due to overdose. And yes, our patients with pain are also becoming addicted to opioids. But it is not clear that the rate of opioid addiction is substantially higher in patients with chronic pain than in patients without pain. Indeed, anyone exposed to opioids has a significant risk of becoming addicted—especially, if they take these drugs at high doses or for long periods of time. Certainly these dangerous levels of exposure to opioids occur more commonly in patients with chronic pain because they have more care encounters when they are experiencing pain.

These issues of excess death and addiction, combined with a lack of any evidence of long-term efficacy, have led many of us in the pain field to question whether opioid should ever be used to treat chronic nonmalignant pain. We know of some patients with chronic pain who are on long-term high-dose opioid therapy who are doing well (ie, have good pain control and good functional status), but these patients are exceedingly rare. Instead, we see large numbers of individuals who want to keep taking opioids, although after we assess them, we conclude that the long-term side effects of these drugs far exceed any benefit they are receiving.

This review highlights why we may see some of the more insidious problems that occur with COT, which are summarized below.

Individuals on COT may continue to “need” opioids to replicate the functions of endogenous opioids that are no longer being released (or are in competition with the exogenous opioids). As the review by Ballantyne and Sullivan states, “a new homeostasis is reached that can only be maintained by continued drug taking”. Individuals on COT lose the ability to endogenously improve mood, decrease stress, and socially engage because the endogenous opioid system becomes inherently less responsive. In pain management, we know of this need for increasing opioid dose over time to maintain analgesia as opioid tolerance. But a similar physiological phenomenon likely occurs with any endogenous opioid function. Although we have mainly anecdotal reports from individuals who have been weaned off of opioids, the change in personality, social engagement, motivation, fatigue, and mood is often profound when individuals on COT successfully taper to lower doses or off opioids. These insidious side effects of COT would all be expected to inhibit individuals from maximally engaging in the patient-centric, disease management strategies that are now recommended for all chronic pain states.

This may also explain why it is often very difficult to taper individuals on COT completely off opioids and underscores the importance of a slow, structured weaning protocol with appropriate psychological support. It may take months or years for endogenous opioid function to return to normal after cessation of opioids, or perhaps this system never returns to normal in some patients (as seems to occur in heroin addicts).

This paralysis of the endogenous opioid system by COT could render ineffective many other treatments that are recommended for chronic pain and that work in part via the endogenous opioid system. Many if not most nonpharmacological therapies for pain, such as exercise, acupuncture, and many other mind-body therapies are believed to work in part by engaging endogenous analgesic pathways that are partly opioid dependent.

Opioids have acute antistress and antidepressant effects, and many of our patients with chronic pain are taking opioids chronically to mediate their co-morbid depression, despair or...
distress more so than to treat pain. Brain imaging studies indicate that many brain regions typically involved in pain and sensory processing are also involved in affective regulation. Patients having chronic pain who show higher degrees of psychological comorbidity or stress might therefore desire opioids because of their temporary salutary effects on these domains, rather than for their intended analgesic effects. We need to develop better cognitive-behavioral and psychosocial interventions that target the needs of the many patients with pain experiencing more harm than benefit from opioids, but still seek these drugs to reduce their affective symptoms.

The endogenous opioid system may actually participate in the pathogenesis of some chronic pain conditions making this class of drugs particularly problematic for some patients. Many lines of evidence suggest that individuals with more centralized pain conditions such as fibromyalgia are particularly unresponsive to opioids, and the endogenous opioid system may be participating in the pathogenesis of these conditions. This has tremendous clinical implications because it means that we may actually make these patients’ pain worse by administering opioids. These same individuals may also be those at highest risk for prolonged use of opioids initially given for acute pain, both because they need higher doses for longer durations, and they are more likely to have the psychological comorbidities that drive unintended use and misuse.

We clearly need to re-think the focus of opioid education and screening programs in light of some of these observations. After any exposure to an opioid, especially following the very common use in the United States for treating acute pain, patients can become addicted or can misuse these drugs to treat concomitant despair, depression, or pain elsewhere in the body that would not be expected to be responsive to an opioid. As we contemplate risk evaluation and mitigation strategies to curb further opioid misuse and addiction, we need to better appreciate these common alternate paths to unintended uses of opioids.

We are not the first field to underappreciate the consequences of hijacking a critical endogenous system for one purpose, only to eventually find that there are significant consequences. Following the discovery of the endogenous corticosteroid system, Hench and others found that cortisone was an extremely effective treatment for rheumatoid arthritis, and this revolutionized our treatment of inflammatory processes. But it took several decades to fully appreciate all of the intermediate and long-term side effects of chronic corticosteroid use. Nearly all of these under-recognized issues were due to off target effects of exogenous corticosteroids on critical endogenous functions of these hormones. Although the short-term effects of opioids have been understood for centuries, long-term, high-dose opioids have only been advocated for a few decades. It is likely that we are now witnessing a similar clinical phenomenon, and as we increasingly appreciate the off-target effects of repurposing a critical endogenous system, the pendulum needs to rapidly swing back towards caution with prescribing a class of drugs that have a plethora of serious side effects other than addiction and death from overdose.

**Conflict of interest statement**

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**References**


