

Long-term opioid therapy unsettles us both coming and going

Mark D. Sullivan

Opioid tapering, like long-term opioid therapy, has turned out to be more complicated than we anticipated. Recently published national data confirm risks of tapering noted in smaller and more localized studies.^{4,8,14} Using pharmacy and medical claims data, Agnoli et al. show that opioid tapers of 15% or more were associated with an increased risk of emergency or hospital encounters for (1) drug overdose or withdrawal and (2) mental health crisis (depression, anxiety, or suicide attempt). Risk was increased for those with higher baseline opioid doses and for those with more rapid tapers.¹ This is ironic. Opioid tapering is intended to reduce the risks of long-term opioid therapy including not only unintentional overdose and opioid use disorder but also depression and suicide. How is it possible that tapering increases the risks it was intended to reduce?

It is important to begin by acknowledging this well-established fact about the endogenous opioid system: Opioids do not function solely as painkillers in the human brain but as general stress modulators.³ Opioids are often called painkillers in the popular press. Pharma sold opioids as targeted treatment for “legitimate pain problems.” Patients embraced the idea that opioids took their pain away while leaving their personalities intact. Prescribers were thankful for a treatment that resolved difficult chronic pain problems, at least for a while. However, endogenous opioids do not only modulate pain but also play an important role in counterbalancing the activating effects of corticosteroids and catecholamines during stress.¹⁷ Indeed, endogenous opioids play a crucial role in promoting survival and maintaining homeostasis by integrating and balancing aversive input and reward.^{12,18} Early research into the endogenous opioid system tended to focus on known exogenous opioid actions, such as pain relief and reward. However, more recent research suggests that these actions are simply the most obvious expressions of a complex and integrated stress modulation opioid system that promotes survival. Many lines of research now point to an essential role for endogenous opioids in socialization and group formation. This social role for endogenous opioids becomes increasingly important and complex as we move from nonprimate mammals to nonhuman primates to humans.¹³ Endogenous opioids support the most important and unique human social functions.⁶ Exogenous opioids may disrupt these

functions, both when they are administered continuously over the long term and when they are withdrawn.¹⁰

Darnall and Fields suggest that attention to patient expectation and agency may be one way to mitigate the risks of opioid tapering.⁵ They remind us that “pain is a predictive cue that signals threat of bodily harm.” Indeed, numerous pain experts now see pain more as a response to threat than damage.⁹ This helps explain why experimental stimuli of rising intensity are more painful than those of falling intensity. In addition, it helps explain why learning can make neutral cues painful or pain relieving. This importance of cognitive threat applies to analgesia as well, for more analgesia is achieved through open than hidden administration of opioids. Darnall and Fields warn us, “If patient expectations are not managed explicitly, the analgesic effect of opioids could be reduced at the most precarious time: precisely when opioid doses are being reduced. In this situation, the likelihood that opioid taper will worsen pain is greatly increased.” This statement seems to make sense but has not been borne out in practice. In our tapering studies, patients are initially fearful of an overwhelming increase in pain with opioid taper but are often pleasantly surprised that pain has not worsened or even improved.¹⁶

Darnall and Fields also point to the importance of patient agency in the experience of pain intensity and analgesia efficacy. Lack of control over acute noxious stimuli is known to increase the intensity of pain experienced. In addition, patient-controlled analgesic pumps have improved postoperative pain care, providing more pain relief with the same or lower opioid dose. Indeed, because self-care is so central to chronic illness care, enhancement of patient agency is an essential element of all chronic care.¹⁵ Whether care is for diabetes or depression or chronic pain, the participation of the patient in the chronic care process must be sought and encouraged.

This raises the thorny issue of voluntary vs involuntary opioid tapers in clinical practice. Darnall and Fields are strong advocates for voluntary opioid tapers: “Patient support for opioid dose reduction is critical.” For both ethical and efficacy reasons, I agree with them. Patient collaboration in the opioid tapering process is valuable and preferred. However, because of patients’ fear of pain and dependence on opioid medications, many opioid tapers are not purely voluntary. Patients on long-term opioid therapy may need to be educated, convinced, cajoled, or even sometimes coerced into opioid taper for their own benefit. A recent overdose, evidence of diversion, or development of significant opioid hyperalgesia may mandate tapering in reluctant patients. Voluntary tapers are preferable, but not always possible. A simple dichotomization of tapers into voluntary and involuntary is neither an accurate nor helpful description of clinical practice.

Darnall and Fields do cite several Medicaid programs that have set firm limits on the daily opioid doses that they will pay for. These limits

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, United States

PAIN 00 (2022) 1–2

© 2022 International Association for the Study of Pain

<http://dx.doi.org/10.1097/j.pain.0000000000002453>

are typically nonnegotiable and therefore not patient-centered. These limits are understandable given the much higher opioid mortality rates found in Medicaid recipients and the complexity of administering cost-constrained Medicaid programs.⁷ However, these firm doing limits were likely formulated before the risks of rapid or high-dose opioid taper were known. Some provision for flexibility or exceptions to these dose limits is now indicated.

Long-term opioid therapy unsettles the delicate balance of our endogenous opioid system that modulates all forms of stress and supports our distinctive human social and emotional functions. Continuous exposure to exogenous opioid medications alters responsiveness to social rewards.¹¹ Tapering these exogenous opioids may unsettle this system again. Normal responsiveness to social and other nondrug rewards may not resume for months.² Patients and families should be educated about and supported through these persistent aspects of opioid dependence. However, in our opioid taper trials, most tapered patients are surprised and thankful not only that their pain has not escalated but also that they no longer feel like “zombies.”

Conflict of interest statement

Dr. Sullivan is a board member of Physicians for Responsible Opioid Prescribing for which he receives no financial compensation.

Article history:

Received 11 August 2021

Accepted 12 August 2021

Available online 16 August 2021

References

- [1] Agnoli A, Xing G, Tancredi DJ, Magnan E, Jerant A, Fenton JJ. Association of dose tapering with overdose or mental health crisis among patients prescribed long-term opioids. *JAMA* 2021;326:411–19.
- [2] Ballantyne JC, Sullivan MD, Koob GF. Refractory dependence on opioid analgesics. *PAIN* 2019;160:2655–60.
- [3] Ballantyne JC, Sullivan MD. The discovery of endogenous opioid systems: what it has meant for understanding pain and its treatment. *PAIN* 2017;158:2290–300.
- [4] Binswanger IA, Glanz JM, Faul M, Shoup JA, Quintana LM, Lyden J, Xu S, Narwaney KJ. The association between opioid discontinuation and heroin use: a nested case-control study. *Drug Alcohol Depend* 2020;217:108248.
- [5] Damall BD, Fields HL. Clinical and neuroscience evidence supports the critical importance of patient expectations and agency in opioid tapering. *PAIN* 2021. doi:10.1097/j.pain.0000000000002443 [Epub ahead of print].
- [6] Dunbar RI. Bridging the bonding gap: the transition from primates to humans. *Philos Trans R Soc Lond B Biol Sci* 2012;367:1837–46.
- [7] Garg RK, Fulton-Kehoe D, Franklin GM. Patterns of opioid use and risk of opioid overdose death among medicaid patients. *Med Care* 2017;55:661–8.
- [8] James JR, Scott JM, Klein JW, Jackson S, McKinney C, Novack M, Chew L, Merrill JO. Mortality after discontinuation of primary care-based chronic opioid therapy for pain: a retrospective cohort study. *J Gen Intern Med* 2019;34:2749–55.
- [9] Legrain V, Mancini F, Sambo CF, Torta DM, Ronga I, Valentini E. Cognitive aspects of nociception and pain: bridging neurophysiology with cognitive psychology. *Neurophysiol Clin* 2012;42:325–36.
- [10] McDonald S, Darke S, Kaye S, Torok M. Deficits in social perception in opioid maintenance patients, abstinent opioid users and non-opioid users. *Addiction* 2013;108:566–74.
- [11] Meier IM, van Honk J, Bos PA, Terburg D. A mu-opioid feedback model of human social behavior. *Neurosci Biobehav Rev* 2021;121:250–8.
- [12] Navratilova E, Atcherley CW, Porreca F. Brain circuits encoding reward from pain relief. *Trends Neurosci* 2015;38:741–50.
- [13] Nummenmaa L, Tuominen L. Opioid system and human emotions. *Br J Pharmacol* 2018;175:2737–49.
- [14] Oliva EM, Bowe T, Manhapra A, Kertesz S, Hah JM, Henderson P, Robinson A, Paik M, Sandbrink F, Gordon AJ, Trafton JA. Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: observational evaluation. *BMJ* 2020;368:m283.
- [15] Sullivan MD. Patient as agent of health and health care. New York: Oxford University Press, 2017.
- [16] Sullivan MD, Turner JA, DiLodovico C, D'Appollonio A, Stephens K, Chan YF. Prescription opioid taper support for outpatients with chronic pain: a randomized controlled trial. *J Pain* 2017;18:308–18.
- [17] Valentino RJ, Van Bockstaele E. Endogenous opioids: the downside of opposing stress. *Neurobiol Stress* 2015;1:23–32.
- [18] White JM. Pleasure into pain: the consequences of long-term opioid use. *Addict Behav* 2004;29:1311–24.