

Persistent Postoperative Opioid Use

Perception, Progress, and Promise

Evan D. Kharasch, M.D., Ph.D., J. David Clark, M.D., Ph.D.

The opioid crisis, related to widespread inappropriate oral opioid prescribing and attendant problems with misuse, diversion, addiction, and overdose deaths, continues to influence anesthesia and surgical practice. The influences are external, such as federal guidelines, state laws, and restrictions by pharmacies, insurers, and healthcare institutions, but are also overtly self-imposed and subconsciously altered behaviors and practices of practitioners regarding opioid use and prescribing.

In addressing opioid use, there is often failure to distinguish between intraoperative opioid use, immediate postoperative opioid prescribing, and convalescent opioid use, and their benefits and risks.¹ While all aspects of opioid use are being appropriately scrutinized, one target receiving considerable attention is postoperative-postdischarge opioids. Prescribing of postsurgical oral take-home opioids at discharge, typically by surgeons, has been recognized as often excessive, creating a reservoir of unused opioids available for diversion and misuse, and this Journal previously called for postdischarge prescribing habits to change.² These changes have occurred coincident with or caused by practitioner awareness, federal guidelines, state prescribing laws, and restrictions by pharmacies, insurers, and healthcare institutions.

A related issue has been the question of persistent postoperative opioid use. A plethora of recent investigations and reviews have tallied prescriptions or filled pharmacy claims,^{3,4} characterized as “persistent postoperative opioid use,” and promoted it as having contributed to the



“We cannot begin to understand or even study ... persistent postoperative opioid use until we can agree on the definition, use common terminology, and even decide if or whether it is a problem.”

opioid crisis. Nevertheless, there is no accepted definition of “persistent postoperative opioid use,” and myriad different definitions abound. The reported incidence of such (mis)labeled, as will be shown below) consequently varies by orders of magnitude. We cannot begin to understand or even study the phenomenon of persistent postoperative opioid use until we can agree on the definition, use common terminology, and even decide if or whether it is a problem. What is persistent postoperative opioid use? How much is too much? How long is too long?

In a much-needed, elegant, and insightful investigation published in this month’s ANESTHESIOLOGY, Jivraj *et al.* begin to inform these questions.⁵ They first asked, what is the variability in the definition of persistent postoperative opioid use and how does it affect the reported incidence across studies? They performed a rigorous systematic literature review to identify definitions of persistent postoperative opioid use. They found 29 different definitions, which were based on written prescriptions, filled prescriptions, or patient-reported consumption with low levels of agreement between these definitions. They then asked, what is the incidence of persistent use as estimated with these different definitions, using a single cohort of 163,000 opioid-naïve postoperative patients? They found that depending on the definition used, estimates of persistent opioid use in the year after surgery ranged from 0.01 to 14.7% of patients, a difference of more than 1,000-fold! Last they asked, what is the ability of each definition to identify patients with opioid-related adverse events? They

Image: Adobe Stock.

This editorial accompanies the article on p. 1528. Michael M. Todd, M.D., served as Handling Editor for this article.

Accepted for publication March 9, 2020. Published online first on March 31, 2020. From the Department of Anesthesiology, Duke University School of Medicine, Durham, North Carolina (E.D.K.); ANESTHESIOLOGY, Schaumburg, Illinois (E.D.K.); Anesthesiology Service, Veterans Affairs Palo Alto Health Care System, Palo Alto, California (J.D.C.); and Department of Anesthesiology, Stanford University School of Medicine, Stanford, California (J.D.C.).

Copyright © 2020, the American Society of Anesthesiologists, Inc. All Rights Reserved. Anesthesiology 2020; 132:1304–6. DOI: 10.1097/ALN.0000000000003298

found that while the specificity of each definition was quite good, ranging from 0.86 to 1.00, the sensitivity was only 0.01 to 0.36. In essence, they found that there is no standard definition of persistent postoperative opioid use, the estimated incidence is enormously dependent on the definition used, and the definitions, therefore, do not provide very actionable information.

The definitional problem identified by Jivraj *et al.* is even greater than previously estimated.⁴ So too is the wide variability in reported estimates of persistent postoperative opioid use among opioid-naïve patients, ranging from 0.01 to 14.7%,⁵ 0.6 to 26%,⁴ and 0.1 to 45% of patients.³ The power of the investigation by Jivraj *et al.* is in the application of the 29 definitions to the same patient population, demonstrating that much if not most of the diversity in published estimates of “persistent postoperative opioid use” apparently derives more from the arbitrary and divergent definitions, rather than differences in populations or actual use. This is methodologic trouble. These ranges are so large that we do not know if there is a major or minor problem, or one at all, or how aggressively to address the problem.

The number and disparity of definitions and incidence range for “persistent postoperative opioid use” are only a small part of the problem. Studies commonly obtain opioid prescription or pharmacy claims data, and use them as a proxy for actual opioid consumption. This is because prescription data are relatively easy and convenient to acquire, and actual use data are labor-intensive and expensive to obtain. The larger problem is that the majority of these studies do not directly measure opioid use at all, and that there has been no careful validation of the use of the “big data” techniques to understand patient-level use—much less the reasons for persistent opioid use. It is well-known that patients prescribed opioid pills at surgical discharge may take only a small fraction,⁶ and we know very little about consumption of subsequently prescribed pills. Moreover, what constitutes “persistence” is variably defined, and ripe for misinterpretation or abuse. As identified by Jivraj *et al.*, the mainstream media commonly describes a patient filling any opioid prescription 90 to 180 days after surgery as “still taking opioids 3 to 6 months later” or who “continues to take drugs for 3 to 6 months after surgery” (*i.e.*, “continued use”), yet a singular prescription in this period may not be continued use at all. Indeed, Jivraj *et al.* identified that 4.7% of patients filled one prescription with 90 to 180 days after surgery, but less than 0.3% filled a prescription that represented 90 days of *continuous* use, a pattern arguably closer to the concept of “continued use” as most would use the term.⁵ Obtaining valid and reliable opioid use data will require more intensive study of substantial cohorts of individual patients. The difficulties inherent in obtaining such data can no longer be accepted as an excuse for not doing so.

The definitional problem and variability in reported estimates of persistent postoperative opioid use^{3–5} are even more problematic because studies do not inform at all on why the opioids were used, even if assuming that they were used. Reports

on “persistent postoperative opioid use” do not identify whether they are taken for surgical pain, preexisting pain, new nonsurgical pain, sleep, or other reasons, or are stored, disposed, or diverted. Additionally, in one small investigation, opioid fills after surgery (“persistent use”) were in fact related to treatment of acute injury-related pain, postoperative complications, follow-up corrective surgery and/or for a different indication than that for which the opioids were started.⁷ It is abundantly clear that many patients may experience persistent postsurgical pain. The incidence of persistent postsurgical pain (10 to 60%) is alarmingly high,^{8,9} can impair recovery, employment, and activities of daily living, and is a major public health problem. How do we interpret a 2 to 3% overall median frequency of “persistent postoperative opioid use”¹⁰ in the context of 10 to 60% frequency of “persistent postoperative pain”? It should also be noted that the rate of persistent opioid use using some definitions approximates the prevailing opioid use in the general population.⁵ Is “persistent postoperative opioid use” a sign of overprescribing, overuse, normal use, and/or misuse, or is it a symptom of persistent postsurgical pain in need of appropriate treatment?

Various pejorative blanket portrayals of “persistent postoperative opioid use” may be a disservice to patients, practitioners, and regulators, particularly when there are multifactorial contributors. The term carries a strong negative connotation, equated with “inappropriate prescribing,”¹¹ “contributing to the opioid epidemic,”⁴ and outright causing “deaths from prescription opioids,”¹² and implies misuse, misbehavior, abuse, or addiction. What is the benefit to patients with legitimate analgesic needs of such “opioid-shaming”? As identified by Jivraj *et al.*, such “opioid shaming” can create anxiety in patients, who may refuse opioids to treat their acute surgical pain for fear of developing addiction, or fear in physicians of opioid prescribing.⁵ The consequence may be inadequately treated pain, chronic postsurgical pain, increased complications, and worse patient outcomes.^{13,14}

The article by Jivraj *et al.* begins to inform the questions of definition and frequency of persistent postoperative opioid use.⁵ However, postoperative opioid prescribing affects not only the patients to whom they are prescribed, but also populations more broadly, due to the pool of opioids potentially available for diversion, misuse, and adverse outcomes. The majority of unused opioids are retained by patients, where they may be used for indications other than prescribed, diverted or stolen, and in turn misused, resulting in addition, overdose, or death. It is important to address the issues of persistent postoperative opioid use, risk to patients from long-term use, and the opioid pool more broadly.

The main challenge at present is to design and execute patient-level studies to understand how, how long, and why opioids are sometimes used persistently after surgery. With a clearer understanding of the magnitude and driving factors for persistent opioid use, we will hopefully move closer to rationally constructing postoperative prescribing guidelines to identify and treat persistent postoperative pain, and avoid any undue risk for developing opioid use disorder. And

similarly, we should aggressively treat acute postoperative pain, to reduce or obviate chronic postsurgical pain, and the attendant need for persistent postoperative opioid use.

Anesthesiologists and surgeons should share in developing a better understanding of opioid use in the period after immediate recovery. This understanding should go beyond counting prescriptions, and should elucidate the drivers and determinants of opioid use, thus providing guidance for optimizing postoperative pain and opioid management. The following is a list to be considered:

- The terms *persistent postoperative opioid use* and *persistent postoperative opioid prescribing* should not be confused, nor should they be used interchangeably.
- There needs to be a clear, rational, and evidence-based definition of persistent postoperative opioid prescribing. It is logical that it continue to be informed by prescription and opioid fill data, but there needs to be a clear definition of persistence (what time period, number of doses or amounts, duration, and continuity) and distinction between prescriptions written and prescriptions filled.
- There needs to be a clear, rational, and evidence-based definition of persistent postoperative opioid use. It must be informed by actual patient use data and have clear definition of persistence (what time period, number of doses or amounts consumed, duration, and continuity). It is critical that associated with use information, there be data on the reason for opioid use (ongoing surgical pain, postoperative complications, follow-up corrective surgery, new unrelated surgical procedure, acute injury-related pain, preexisting pain, sleep, avoidance of withdrawal, or other indication).

Incorporating agreed upon definitions into our research efforts will at the very least facilitate the development of a coherent understanding of how opioids are prescribed and used after surgery. Guidance based on such knowledge will likely be more informed, successful, and accepted than that arbitrarily imposed by legislators, regulators, and insurance companies.

Research Support

Support was provided by National Institutes of Health (Bethesda, Maryland) grant No. R01 DA042985 (to Dr. Kharasch), No. R01 NS094438 (to Dr. Clark), and Department of Veterans Affairs (Washington, D.C.) grant No. I01 BX000881 (to Dr. Clark).

Competing Interests

Dr. Kharasch is the Editor-in-Chief of *ANESTHESIOLOGY*, and his institution receives salary support from the American Society of Anesthesiologists (Schaumburg, Illinois) for this position. Dr. Clark has a consulting agreement with Teikoku Pharma USA (San Jose, California).

Correspondence

Address correspondence to Dr. Kharasch: evan.kharasch@duke.edu

References

1. Kharasch ED, Avram MJ, Clark JD: Rational perioperative opioid management in the era of the opioid crisis. *ANESTHESIOLOGY* 2020; 132:603–5
2. Kharasch ED, Brunt LM: Perioperative opioids and public health. *ANESTHESIOLOGY* 2016; 124:960–5
3. Pagé MG, Kudrina I, Zomahoun HTV, Croteau J, Ziegler D, Ngangue P, Martin E, Fortier M, Boisvert EE, Beaulieu P, Charbonneau C, Cogan J, Daoust R, Martel MO, Neron A, Richebe P, Clarke H: A systematic review of the relative frequency and risk factors for prolonged opioid prescription following surgery and trauma among adults. *Ann Surg* 2020; 271:845–54
4. Kent ML, Hurley RW, Oderda GM, Gordon DB, Sun E, Mythen M, Miller TE, Shaw AD, Gan TJ, Thacker JKM, McEvoy MD; POQI-4 Working Group: American Society for Enhanced Recovery and Perioperative Quality Initiative-4 joint consensus statement on persistent postoperative opioid use: Definition, incidence, risk factors, and health care system initiatives. *Anesth Analg* 2019; 129:543–52
5. Jivraj NK, Raghavji F, Bethell J, Wijeyesundera DN, Ladha KS, Bateman BT, Neuman MD, Wunsch H: Persistent postoperative opioid use: A systematic literature search of definitions and population-based cohort study. *ANESTHESIOLOGY* 2020; 132:1528–39
6. Bicket MC, Long JJ, Pronovost PJ, Alexander GC, Wu CL: Prescription opioid analgesics commonly unused after surgery: A systematic review. *JAMA Surg* 2017; 152:1066–71
7. Callinan CE, Neuman MD, Lacy KE, Gabison C, Ashburn MA: The initiation of chronic opioids: A survey of chronic pain patients. *J Pain* 2017; 18:360–5
8. Perkins FM, Kehlet H: Chronic pain as an outcome of surgery. A review of predictive factors. *ANESTHESIOLOGY* 2000; 93:1123–33
9. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: Risk factors and prevention. *Lancet* 2006; 367:1618–25
10. Pagé MG, Clarke H, Kudrina I: Response to the comment on “postoperative opioid prescribing and pain.” *Ann Surg* 2020; 271:e125–6
11. Neuman MD, Bateman BT, Wunsch H: Inappropriate opioid prescription after surgery. *Lancet* 2019; 393:1547–57
12. Glare P, Aubrey KR, Myles PS: Transition from acute to chronic pain after surgery. *Lancet* 2019; 393:1537–46
13. Gan TJ: Poorly controlled postoperative pain: Prevalence, consequences, and prevention. *J Pain Res* 2017; 10:2287–98
14. van Boekel RLM, Warlé MC, Nielen RGC, Vissers KCP, van der Sande R, Bronkhorst EM, Lerou JGC, Steegers MAH: Relationship between postoperative pain and overall 30-day complications in a broad surgical population: An observational study. *Ann Surg* 2019; 269:856–65