

Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M., Editor

Perioperative Opioids and Public Health

Evan D. Kharasch, M.D., Ph.D., L. Michael Brunt, M.D.

ANESTHESIOLOGISTS and surgeons face three challenges in the quest to provide optimum perioperative pain care, particularly within the growing domain of “shared responsibility” for patients’ surgical outcomes with other physicians and providers. Two challenges are well known, and the third may not have yet registered in the collective conscience of the specialties.

The first challenge is provision of adequate perioperative analgesia. Adequate pain relief has been deemed a fundamental right,¹ but a plurality (more than 80%) of patients report inadequate postoperative pain relief.^{1–4} Adequate postsurgical pain treatment affords better patient and economic outcomes,⁵ whereas acute postoperative pain causes suffering, morbidity, and the risk of chronic postsurgical pain.^{6,7} Acute postoperative pain is a major risk factor for chronic postoperative pain, which occurs in 10 to 50% of patients.⁶ Moreover, the incidence of inadequately treated postoperative pain seems unimproved over the past two decades.^{4,8}

For postoperative pain management, many unresolved issues, unmet needs, and unanswered questions that define a research agenda were previously articulated.^{9,10} Emphasis on multimodal approaches to postoperative pain therapy has grown,^{11,12} yet multimodal safety and the ideal regimen(s) are undefined.¹³ Opioids remain the primary systemic pharmacotherapy for intraoperative and postoperative analgesia, particularly for moderate to severe pain.

The second challenge is to minimize or prevent opioid-related side effects—the most serious of which is respiratory depression.^{14,15} The incidence of respiratory depression after major surgery was 0.3, 1.1, or 17% using requirement for naloxone, hypoventilation, or oxygen desaturation as indicators, respectively, even in those using patient-controlled

analgesia.¹⁶ The consequence and importance of postoperative respiratory depression have been highlighted often by the Anesthesia Patient Safety Foundation.¹⁷

The third issue is the soaring volume of opioid prescribing, prescribing patterns, and the accompanying devastating surge in prescription opioid diversion, abuse, addiction, and overdose (fig. 1¹⁸). The US Centers for Disease Control and Prevention defined prescription drug abuse as an epidemic¹⁹ and one of its top five health threats for 2014.²⁰ Numerous other US federal agencies (*e.g.*, Office of National Drug Control Policy and the National Drug Control Strategy, Substance Abuse and Mental Health Services Administration, National Institutes of Health, Food and Drug Administration, Drug Enforcement Administration) are intently focused on diversion, abuse, addiction, and their consequences. Opioid sales quadrupled between 1999 and 2010, and it has been stated that “the system is awash in opioids.”²¹ The United States has the highest opioid use per capita in the world, and it alone consumes 80% of the world’s opioids; nevertheless, these problems are not limited to the United States.^{22,23}

The toll of prescription opioid abuse is both human and financial. Myriad alarming and saddening statistics abound. Approximately 5 million Americans report using prescription pain relievers nonmedically (*i.e.*, without a prescription or medical need),²⁴ and the rate has risen dramatically over the last two decades (fig. 2). Prescription opioids were involved in more than 16,600 overdose deaths in the United States in 2010 or approximately 45 deaths every day.²⁵ Such deaths more than quadrupled between 1999 and 2010,²⁶ and, since 2003, more overdose deaths involve prescription opioid analgesics than heroin and cocaine combined.¹⁹ Moreover, for every unintentional fatal opioid analgesic

This article is featured in “This Month in Anesthesiology,” page 1A. Figures 1 to 3 were enhanced by Annemarie B. Johnson, C.M.I., Medical Illustrator, Vivo Visuals, Winston-Salem, North Carolina.

Submitted for publication September 15, 2015. Accepted for publication November 13, 2015. From the Division of Clinical and Translational Research, Department of Anesthesiology, Washington University in St. Louis, St. Louis, Missouri (E.D.K.); Department of Biochemistry and Molecular Biophysics, Washington University in St. Louis, St. Louis, Missouri (E.D.K.); Department of Surgery, Section of Minimally Invasive Surgery, Washington University in St. Louis, St. Louis, Missouri (L.M.B.); and The Center for Clinical Pharmacology, St. Louis College of Pharmacy and Washington University in St. Louis, St. Louis, Missouri (E.D.K.).

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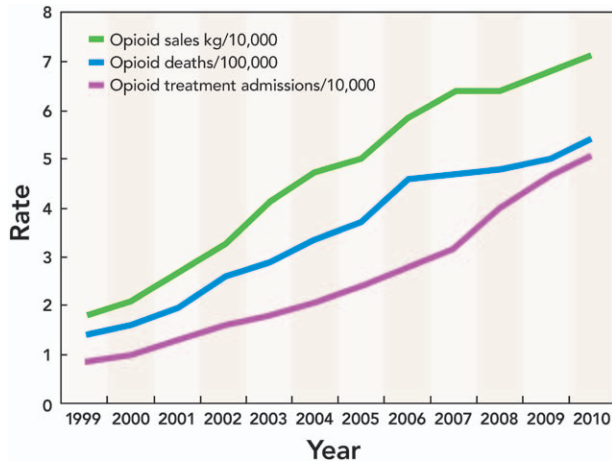


Fig. 1. Rates of opioid analgesic sales, unintentional overdose deaths, and addiction treatment admissions, 1999 to 2010. Data from Kolodny *et al.*¹⁸ and redrawn with permission. Adaptations are themselves works protected by copyright. So to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

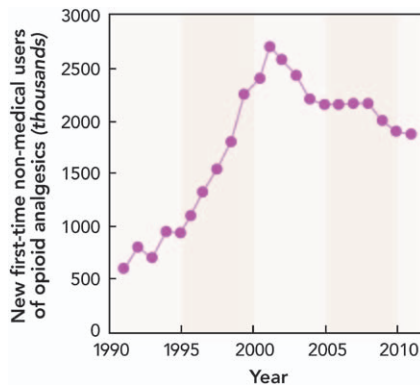


Fig. 2. Number of new first-time nonmedical use of opioid analgesics. Data from Kolodny *et al.*¹⁸ and redrawn with permission. Adaptations are themselves works protected by copyright. So to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

overdose, 9 others are admitted for substance abuse treatment, 35 visit emergency departments, 161 report drug abuse or dependence, and 461 report nonmedical uses of opioid analgesics.¹⁹ In 2011, an estimated 700,000 people in the United States received treatment for misuse of prescription pain relievers, exceeding the number for cocaine (511,000), heroin (430,000), or tranquilizers (300,000), and there were 488,000 emergency department visits involving nonmedical use of prescription opioids.²⁷ Visits for opioid overdose are also associated with a higher likelihood of future hospitalization and near fatal events.²⁸ The economic cost to US society of nonmedical use of prescription opioids has been estimated to exceed \$70 billion annually, including health care, workplace, and criminal justice costs.^{26,29–31}

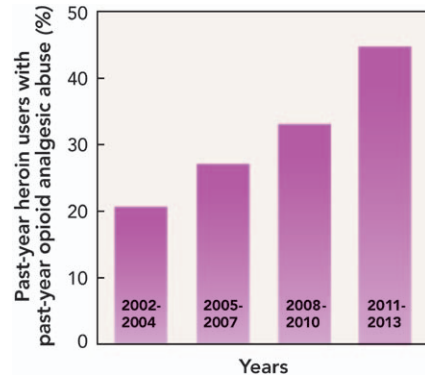


Fig. 3. Past-year heroin users with past-year opioid analgesic abuse. Data from Jones *et al.*³⁶ and redrawn with permission. Adaptations are themselves works protected by copyright. So to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

This rising epidemic of prescription opioid abuse over the past two decades has also changed the demographics of heroin abuse.^{32–34} Once used primarily by young inner-city minority males, more recent heroin users are older nonurban men and women, who first came to heroin use through prescription opioids and/or who are using heroin as a cheaper and more accessible alternative to prescription opioids.³⁴ Indeed, more heroin-dependent users today started with prescription opioids (65%) than heroin (35%) as their first opioid of abuse—a dramatic change from the 1960s when the number was less than 20%.³⁴ More recently shown is that switching from prescription opioids to heroin, or to heroin plus prescription opioids, is common and increasing, primarily for practical reasons such as accessibility and cost.³⁵ According to the Centers for Disease Control and Prevention, the percentage of heroin users with opioid pain reliever abuse or dependence doubled from 21% in 2004 to 2007 to 45% in 2011 to 2013 (fig. 3), and, among heroin users, opioid analgesic use was more common than alcohol, marijuana, or cocaine.³⁶ In another study, four of five heroin initiates reported that their use began with prescription opioids.³² Moreover, the incidence of heroin use is 19 times greater among those who have abused prescription pain drugs than among those who have not.³² Prescription opioids have become regarded as a “gateway drug” to heroin!

The ubiquitous supply of oral opioids available for diversion feeds the problem. An estimated 4 to 20% of all opioid pills prescribed in the United States are used nonmedically—nearly half a billion doses per year.³⁷ Although “prescription shopping” by abusers has been highlighted in the lay press, the primary source of abused prescription opioids is “friends and family.”^{38,39} Among nonmedical users, more than 80% obtain opioids from friends or relatives, whereas only 10 to 20% obtain them from a physician.^{40,41} In the United States, among those who used pain relievers nonmedically in 2011 to 2012, 78% used drugs intended for someone else, and only 20% obtained them from their own physician.²⁴ Most

(69%) obtained them from a friend or a relative (54% for free, 11% by purchase, and 4% without asking); only 4% from a drug dealer or other stranger; and 1% by theft from a doctor's office, clinic, hospital, or pharmacy, or by Internet purchase.²⁴ Availability of unused or leftover prescription opioids is so prevalent that young recreational users do not have to venture outside their immediate social networks to find those who will sell or share pills.⁴¹ Pharmacy take-back programs for disposal of unwanted leftover opioids, designed to reduce the pool,^{42,43} have not to date succeeded.⁴⁴

Clearly, the diversion of unused prescription opioids for nonmedical use is rampant. Yet the healthcare system itself is the source of these opioids. Both the extent of diversion and the nonmedical use of opioids are proportional to their prescriptive availability.⁴⁵ More than 80% of nonmedical users who received opioids for free from friends or family said that their source had originally obtained them from a doctor.²⁴

The greatest regulatory, medical, and scientific focus on nonmedical prescription opioid use, dependence, diversion, and harm has been on chronic opioid use, particularly for chronic noncancer pain.^{46,47} The highest risk opioid users are those receiving high doses, seeking prescriptions from multiple providers, and likely to be involved in diversion.¹⁹ In this realm, key data gaps and research agendas have been identified regarding the public health issues associated with opioid analgesics for chronic nonmalignant pain.⁴⁸

In contrast, there has been little attention devoted to nonmedical use of opioids prescribed for postoperative use, and there is a dearth of data, information, and knowledge. Is there an issue? How big? Whose issue? Our issue? And even if not ours, or ours exclusively, could it be ours to help solve?

Relatively little is known about the patterns of postsurgical opioid analgesic use.⁴⁹ How many million opioid doses are prescribed annually for acute postoperative pain? How many are consumed by the patients for whom the prescription was written? How many are used by such patients for nonmedical reasons? How many are diverted, intentionally or unintentionally, knowingly or unknowingly, for use by others? What is the relationship between prescribing patterns and actual opioid use after discharge from surgery? How big is the problem? And what are the adverse consequences? How many individuals who receive opioids for acute postoperative pain become addicted to opioids? How much of the 3 to 7% incidence of prolonged opioid use after surgery⁴⁹⁻⁵¹ represents treatment for persistent postoperative pain *versus* inappropriate use? It is important to identify the key data gaps and develop research agendas regarding nonmedical use of opioids prescribed for postoperative pain.

The issue here is *not* the use of opioids for postoperative pain. The question is to what extent overprescribing of postoperative opioids is creating a reservoir of unused drug, with the potential or consequence of opioid sharing, selling, and diversion. The limited data available do suggest that there is a problem. Patients may cease taking opioids before their pain is resolved⁵⁰ or have leftover opioids when their pain

is resolved. Among 213 urologic patients postoperatively prescribed an average of 25 opioid pills, only 58% of pills were consumed, 67% patients had leftover drug, and more than 90% of patients kept their unused opioid.⁵² Among 287 patients undergoing upper extremity surgery, half reported using postoperative opioids for only 2 days or less, stopping because of little or no pain.⁵³ The postoperative analgesic prescription was for 30 tablets, but 77% of patients took 15 or fewer, 45% took fewer than 5, and some took none. On average only 11 tablets were consumed, leaving 19 per patient leftover—a total of 4,639 unused tablets. After dermatologic surgery, one third of patients prescribed opioids did not take them, 86% has leftover pills, and half of those patients planned to keep them.⁵⁴

It is not unusual in the co-author's (L.M.B.) experience in minimally invasive surgery to see patients prescribed 40 or 50 oxycodone tablets postdischarge, and to have them return to clinic and state that they took pain pills for only 1 or 2 days postoperatively or even not at all. This highlights an opportunity for investigations to better understand patients' pain experiences and actual opioid use after specific operations, and to develop best practices guidelines and dissemination and implementation strategies for residents' and other providers' education, so that prescribing patterns are tailored based on the actual usage patterns. Another factor that may influence larger numbers of opioids being prescribed postoperatively is the desire to reduce the burden of pain medication renewal phone calls to a surgeon's office after discharge. This too may be amenable to influence if better opioid use data are available.

Opioid diversion may occur through a variety of mechanisms. Although seemingly innocuous, leftover opioids are ripe for diversion through residential burglaries; medicine cabinet thefts by relatives, visitors, cleaning and repair personnel; and theft by hotel staff, as well as gift or sale by "friends and family."⁵⁵ The goal should be to have less unused opioid available for diversion and misuse, without at all compromising the effectiveness and availability of postoperative analgesia.

What can, and what should, anesthesiologists and surgeons do to help address and mitigate the escalating problem of opioid availability, diversion, nonmedical use, and opioid-related harm? Having traditionally trod carefully between pain treatment (including patient satisfaction and bothersome phone calls) and opioid side effects, it is even more important now to navigate between analgesia, side effects, and the opioid epidemic.

It is time to articulate the unresolved issues, unmet needs, and unanswered questions that will define a research, dissemination, and implementation agenda. The sea change from inpatient to short-stay and ambulatory surgery has exacerbated the issue. How do we implement improved postoperative pain relief in the face of diminishing resources?⁴ How do we comprehensively evaluate procedure-specific multimodal analgesic strategies' effectiveness and safety and identify

ideal regimens?¹³ How do we best implement regional anesthetic techniques, indwelling catheters, long-duration local anesthetics, antiinflammatory medications, and other approaches? How do we devise regimens, optimize drug selection, and deliver care that provide not only satisfactory intraoperative and immediate postoperative analgesia, but also ideally, confer longer lasting benefit? More specifically, how do we thoughtfully examine and optimize rational opioid use and selection, and how do we define systems-level approaches to optimal opioid use?^{9,10}

During the past decades, there has been a trend, or fashion, toward the use of shorter and shorter duration opioids intraoperatively, particularly in ambulatory surgery.⁵⁶ Is this the best approach? Is opioid-induced hyperalgesia from ultrashort-duration opioids a problem?^{57–59} Several investigations, in both surgical patients and volunteers, have shown that high-dose opioid infusions, particularly remifentanyl, are associated with greater postoperative pain and opioid consumption or with postinfusion hyperalgesia. By using ultrashort-duration opioids, are we inadvertently causing more postoperative pain and necessitating greater postoperative opioid use?⁵⁷ Is remifentanyl hyperalgesia associated with persistent postoperative pain?⁵⁹ Are we inadvertently encouraging surgeons to prescribe more take-home opioids? Should we instead be using long-duration intraoperative opioids that also diminish postoperative pain? And perhaps, therefore, also diminish postoperative opioid requirements and prescribing? Intraoperative methadone decreases postoperative pain and postoperative opioid consumption^{60–62} and might offer a solution, although methadone effectiveness and safety in outpatients has not been evaluated, and warrants investigation.

By devising intraoperative anesthetic regimens and surgical (minimally invasive) approaches that diminish postoperative pain, can we reduce the need for postoperative opioids, postoperative take-home opioid prescribing, and the potential for untoward use and diversion? And, if successful, can we communicate to the prescribers of these postoperative opioids that patients need less and should receive less?

Let us acknowledge the problem of opioid diversion and misuse, develop a better understanding of whether perioperative opioid use and postoperative prescribing may contribute to the problem, and optimize rational opioid selection and therapeutic application.

Note Added in Proof: Recently released Centers for Disease Control and Prevention data show that the problem continues to worsen: From 2013 to 2014, US opioid overdose deaths increased 14%, causing 61% of all overdose deaths (28,647 deaths—one every 18 min!). Deaths involving natural and semisynthetic opioids (*e.g.*, morphine, oxycodone, hydrocodone) increased 9%, those involving synthetic opioids (*e.g.*, fentanyl, tramadol, excluding methadone) increased 80%, and heroin-related deaths increased 26% (more than tripling over the last 4 yr). This epidemic of opioid overdose deaths is due to two interrelated trends:

a 15-yr increase (triple) in deaths involving prescription opioids, and a recent surge in heroin-related deaths (due in turn primarily to prescription opioids, because past prescription opioid misuse is the strongest risk factor for heroin initiation and use).⁶³

Acknowledgments

The authors thank Henrik Kehlet, M.D., Ph.D., Section for Surgical Pathophysiology, Rigshospitalet, Copenhagen, Denmark, for his very helpful discussions and suggestions on the issues in this article.

This study was supported by National Institutes of Health (Bethesda, Maryland) grants R01-DA14211 and R01-DA25931.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Kharasch: Department of Anesthesiology, Washington University in St. Louis, 660 S Euclid Ave, Campus Box 8054, St. Louis, Missouri 63110 kharasch@wustl.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY'S articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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