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Opioids and Public Health: The Prescription Opioid Ecosystem and Need for Improved Management

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ABSTRACT

While U.S. opioid prescribing has decreased 38% in the past decade, opioid deaths have increased 300%. This opioid paradox is poorly recognized. Current approaches to opioid management are not working, and new approaches are needed. This article reviews the outcomes and shortcomings of recent U.S. opioid policies and strategies that focus primarily or exclusively on reducing or eliminating opioid prescribing. It introduces concepts of a prescription opioid ecosystem and opioid pool, and it discusses how the pool can be influenced by supply-side, demand-side, and opioid returns factors. It illuminates pressing policy needs for an opioid ecosystem that enables proper opioid stewardship, identifies associated responsibilities, and emphasizes the necessity of making opioid returns as easy and common as opioid prescribing, in order to minimize the size of the opioid pool available for potential diversion, misuse, overdose, and death. Approaches are applicable to opioid prescribing in general, and to opioid prescribing after surgery.

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The current opioid crisis, emanating from inappropriate prescribing, marketing, diversion, and misuse of oral prescription opioids for acute and chronic noncancer pain,[1] has a staggering human and economic toll.[2–4] In the United States, there have been more than 450,000 opioid-related deaths over the past two decades, one quarter of which may be suicides.[5] This cost the U.S. economy more than $2.5 trillion between 2015 and 2018, including an estimated $700 billion to $1 trillion in 2018 alone—representing 3.4% of the U.S. gross domestic product.[6] Opioid misuse and fatal overdose are not limited to the United States,[7–10] or to adults.[11] Moreover, the problem worsened during the COVID-19 pandemic, due primarily to illicit fentanyl and analogs.[12–14] The influence of the COVID-19 pandemic on opioid overdose, whether due to illicit fentanyl abundance, disrupted prescription drug supply chains, increasing drug toxicity, social isolation, unemployment, worsening mental or physical health, or reduced access to emergency medical and drug treatment services, continues well into 2021.[15,16]

The opioid crisis has multiple antecedents.[17–19] It is grounded on the pain epidemic, currently the most prevalent (40 to 100 million U.S. adults), disabling, and costly public health problem in the United States, the societal costs of which exceed the annual combined costs of heart disease, diabetes, and cancer.[20] It is also grounded on the more debilitating subset of high-impact chronic pain, which impairs work outside the home, education, social activities, and simple self-care and daily living, and is suffered by 11 million U.S. adults, and who use a disproportionate amount of health care.[21] It is also grounded on the overprescription and overuse of oral opioids, and in patients for whom they were not indicated or effective. Contributory also were avaricious and illegal marketing of prescription oral opioids, and economic stagnation, unemployment, poverty, lack of opportunity, social distress, and substandard living and working conditions in underprivileged areas of the country.[22,23] The U.S. Drug Enforcement Administration (Springfield, Virginia) estimates that 163,683,029 schedule II prescriptions (retail cost $11.8 billion) were filled for "acute pain" in 2017.[24] Overuse and misuse of prescription oral opioids and associated overdose were then followed by a rapid and fluid shift of the use- and supply-chain of abused opioids from medical to illicit (first heroin and then fentanyl) sources.[25–27] Indeed, deaths in North America attributed to illicit fentanyl now outnumber those from heroin.[19]

The "opioid paradox" is that opioid overdose mortality has continued to increase despite steady reductions in opioid prescribing (fig. 1).[31] Overall opioid prescribing is decreasing, in both numbers of patients exposed and average doses prescribed (fig. 1).[30,32] Opioid prescribing in the United States initially quadrupled from 1999 to the peak in 2012,[33] but has decreased 43% since then (from 81 to 47 prescriptions per 100 persons in 2020).[30] Nonetheless, average daily morphine milligram equivalents have decreased more slowly, because the average supply per prescription continues to rise.[34] Opioid use is still common, with 15% of the U.S. population filling one or more opioid prescriptions in 2018.[34] Despite the declining prescription numbers, overdose deaths have not declined, due to the increased use of heroin and illicit fentanyl.[35,36]

There are inescapable public and practitioner awareness of the opioid crisis, extensively documented inappropriate

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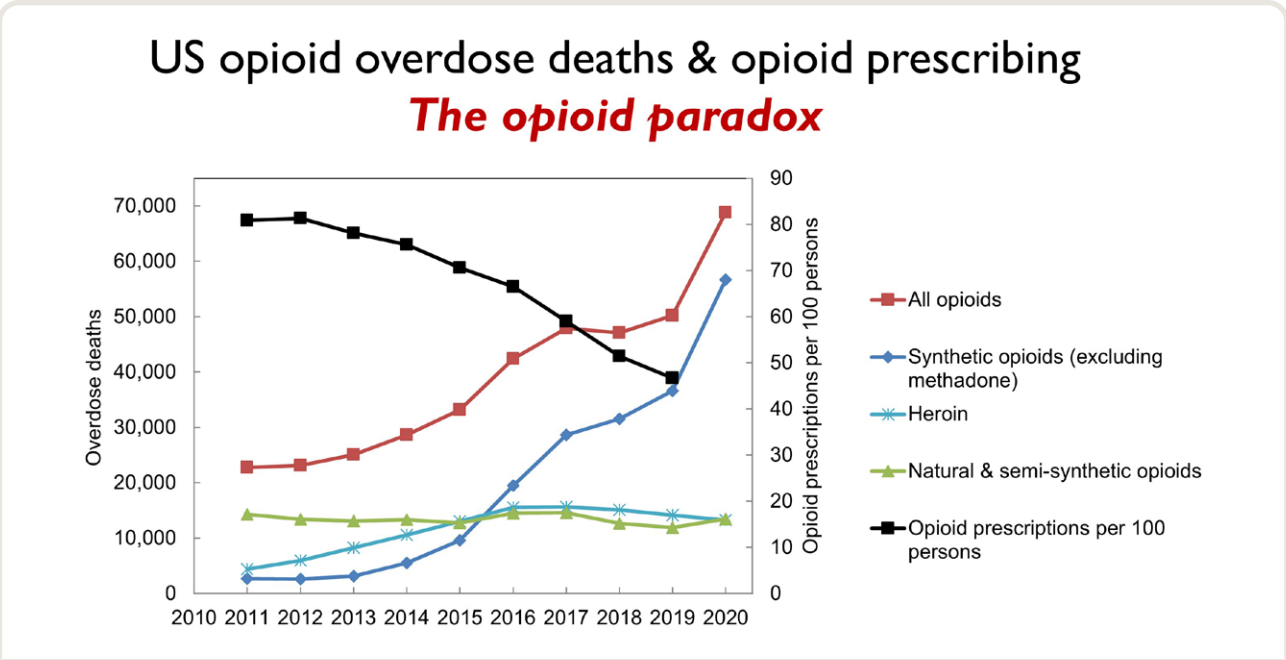

Fig. 1. The opioid paradox. Opioid prescriptions are declining while opioid overdose deaths are increasing.[28,29,30]

outpatient oral opioid use and overprescribing, innumerable federal, state, local, and institutional regulatory, legislative, and guidance restrictions on opioid prescribing, and billions of dollars invested to combat the opioid crisis over the past 5 yr. Nonetheless, these approaches are failing to retard or reverse the epidemic of opioid-related fatalities. There has been some improvement, in that the number of Americans 12 yr or older who misused opioids decreased from 11.8 million in 2016 to 10.1 million in 2019,[37,38] and the number who misused prescription pain relievers decreased from 11.5 million in 2016 to 9.7 million in 2019.[37,38] In addition, the number who initiated prescription pain reliever misuse *each day* in 2019 (4,400)[38] was less than in 2018 (5,230).[39] Nevertheless, this still represents 1.6 million new misusers in just 1 yr. Moreover, these small reductions represent a feeble response compared with the plethora of recently enacted restrictive countermeasures intended against opioid prescribing and misuse.

Furthermore, the opioid overdose rate is climbing (fig. 1). Nearly 50,000 Americans died of an opioid overdose in 2019 (137 per day), then a new record.[28,40] This was a threefold increase from 16,600 overdose deaths in 2010,[41] and a fourfold increase from the previous decade.[42] Even worse, opioid overdose deaths spiked again in 2020, to 66,000 (181 per day, 1 every 8 min),[28] the highest number on record and the largest annual percentage increase in the past 20 yr. Opioids now account for 74% of all fatal drug overdoses, increased from 63% in 2015.[29] Death rates continue to be driven primarily by overdose from synthetic opioids (mainly illicit fentanyl), which account for more than two thirds of opioid overdose deaths.[40] Overdose due to prescription opioids has plateaued (fig. 1), but overdose death rates involving fentanyl and other synthetic opioids increased more than *10-fold* from 2013 to 2019,[40] and *more than doubled* between 2016 and 2020.[28] Most recently, synthetic opioid deaths increased 38% in the year ending May 2020,[13] and continue to rise.[28] It is abundantly clear that current approaches to the opioid crisis are not succeeding.

Postoperative Pain and Opioids: The Problem of Variability

The seminal and intractable problem is inter- and intrapatient variability in postoperative pain and pain relief. Distinct and widely disparate trajectories of postoperative pain and recovery have been identified.[43,44] Postoperative pain and opioid needs can be influenced by ethnic, racial, physiologic, cultural, and religious factors, as well as by age, sex, comorbidities, fear, anxiety, previous pain history, coping style, drug interactions, genetics, health disparities, health literacy, preoperative opioid use, social support, and setting (inpatient *vs.* outpatient surgery).[45] Considerable variability in postoperative pain and opioid consumption is a consistent finding. For example, across four common operations (laparoscopic cholecystectomy, hernia repair, hip replacement, knee replacement) and 103 hospitals, postoperative pain was common and highly variable (range, 0 to 9 on a 10-point scale).[46] Among nearly 2,400 patients across 12 surgical procedures, there was 25-fold variability in the interquartile range of opioid pills taken after surgery.[47] After Cesarean section, many patients took no or less than 5 opioid pills, while about 20% took all or nearly all of the

approximately 30 pills prescribed at discharge,[48,49] and after thoracic surgery, nearly half took no or less than five opioid pills, while nearly 30% took all or nearly all.[48]

Variability in postoperative pain and opioid use is accompanied by considerable variability in postsurgical opioid prescribing. Indeed, such variability is even greater for surgical than for medical conditions.[45] For example, in adults, after total knee arthroplasty, the interquartile range of postdischarge oral opioids prescribed to opioid-naïve patients was 75 to 475 mg morphine equivalents, and the total range was 0 to 1,500 mg.[50] In children, after the common outpatient operations tonsillectomy and hernia repair, postsurgical opioid prescribing is similarly highly variable.[51] This is reflected in numerous other procedures as well, in both adults[52] and children.[53] Variability is great even among members of the same surgical team, and between provider type. For example, after discharge from five common inpatient surgical procedures, ranges of 6 to 72, 6 to 189, and 5 to 1,000 opioid pills, equivalent to 30 to 600, 30 to 1,600, and 25 to 1,000 morphine milligram equivalents, were prescribed by attending surgeons, residents, and advanced care practitioners, respectively.[54] Variability in postoperative opioid prescribing is also influenced by surgeons' years of practice, credentialing, type of surgery, and geographic location.[55] Variability ranges from micro scale (within the same surgery service in just one hospital),[56] to macro scale (across countries and continents).[57]

The Opioid Pool

A foundational element of the opioid crisis is the size of the unused opioid pool available for potential diversion, misuse, addiction, and overdose. The pool is fed by the overprescription of oral opioids, including the aforementioned inappropriate outpatient use of oral opioids for acute and chronic noncancer pain. Many patients have leftover unused opioid pills, regardless of the indication for which they were prescribed. For example, a survey of more than 1,000 U.S. adults with recent opioid use reported that 57% had or expected to have leftover pills, and 49% planned to keep them for future use.[58]

Also contributory is the overprescription of oral take-home opioids after surgery, a problem reviewed previously in this journal,[59] and repeatedly documented further thereafter.[47,50,52,60–66] Surgeons prescribe approximately 10% of all opioids (and another 6% by dentists), and while this pales in comparison to the 33% prescribed by family practitioners and internists, surgical prescribing accounts for millions of patients and tens of millions of unused pills left over each year.[67] For example, among nearly 2,400 patients and 12 surgical procedures, a median of 30 postsurgical take-home opioid pills was prescribed per patient, and 19 pills were left over unused.[47] A recent large meta-analysis of 44 studies involving 13,068 patients found that an average 61% (95% CI, 56 to 67%) of postoperative opioids were leftover, equivalent to 582,000 5 mg hydrocodone tablets prescribed, and 355,000 tablets left over, or 27 tablets left over per person.[65]

Most patients do not return or dispose of unused prescription opioids, and do not store them in locked or inaccessible locations.[49,58,62,63,68–70] Leftover opioids may be used to self-medicate for indications other than those for which they were prescribed, voluntarily diverted to others for pain relief or other use, illegally diverted by theft, or accidentally ingested by toddlers, with consequent risks of misuse, abuse, addiction, and overdose.

Children and adolescents comprise a vulnerable population affected by the size and availability of the opioid pool.[71] Adolescent opioid misuse may lead to dependence, opioid use disorders, heroin use, and overdose.[71,72] In 2019, approximately 670 adolescents (12 to 17 yr) and 1,100 young adults (18 to 25 yr), compared with 2,625 adults (26 yr and older) initiated prescription opioid misuse *each day*.[38] Opioid-related pediatric hospitalizations doubled from 2004 to 2015.[73] One third were less than 6 yr old, suggesting accidental ingestion, and two thirds were 12 to 17 yr, suggesting deliberate misuse.[73] Adolescents freely divert prescription opioids.[71] The source of prescription opioids misused by adolescents (12 to 17 yr) differs from the population as a whole, and diversion is even more important than in adults. Misused opioids are obtained by diversion (from a friend or relative for free, purchase, or theft) more by adolescents (58%) than adults (51%) and less from prescription by adolescents (28%) than adults (37%.).[38,71] Opioids are found in more than one third of adolescents' homes, and many parents and caregivers are unaware of the risk they pose.[74] It is clear that current efforts to decrease adult opioid use have not diminished opioid exposure to children.[66,73,75]

The combination of outpatient opioid overprescribing, large amounts of unused opioids, retention for future use, and storage in unsecured accessible locations creates a vast risk space of hundreds of millions of opioid pills,[76] and opportunity for potential harm. This constitutes the opioid pool.

Managing the Size of the Opioid Pool

There are three general approaches to managing the size of the opioid pool. These are supply-side, demand-side, and disposal (fig. 2).

Supply-side Opioid Management

Supply-side regulation targeting restricted prescribing has been the overwhelmingly predominant focus of efforts to combat the opioid crisis. U.S. opioid prescribing is influenced by myriad laws, regulations, policies and guidelines, from numerous federal government agencies (*e.g.*, Centers for Disease Control and Prevention, Atlanta, Georgia; Veterans Affairs Healthcare System; Department of Defense; Centers for Medicare and Medicaid Services, Baltimore,

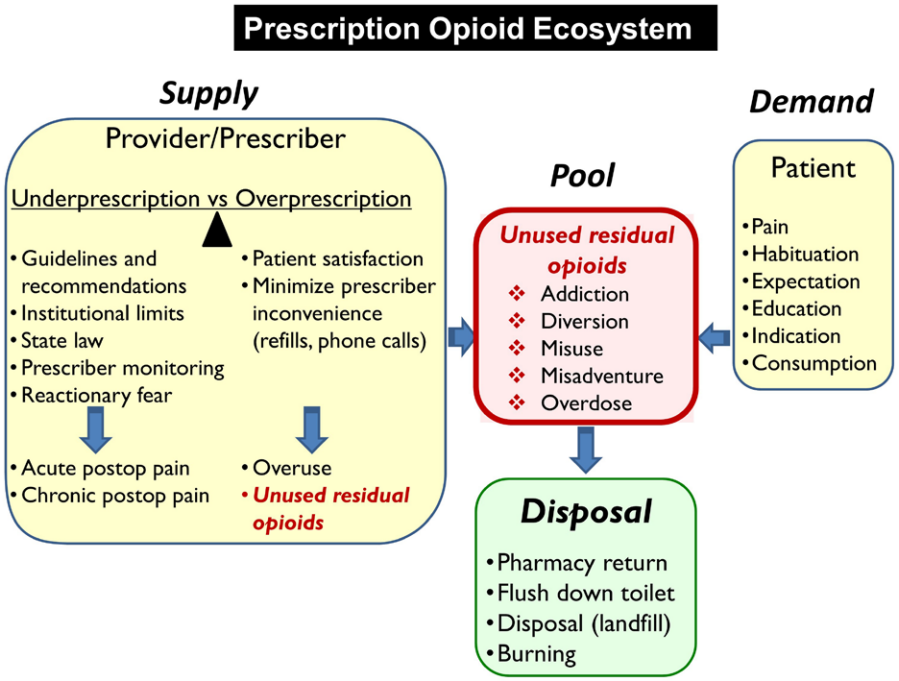

Fig. 2. The prescription opioid ecosystem. The pool of unused prescription opioids available for diversion, misuse, and overdose is influenced by supply, demand, and return or disposal. Overprescription of opioids, while providing sufficient supply to treat pain, risks potential patient overuse or residual unused opioids, and underprescription risks undertreated acute and chronic pain. Reducing supply alone has not been successful at reducing opioid overdose rates. Reducing demand through better pain treatment, and enhancing disposal and return, are additional approaches to reducing the opioid pool and mitigating opioid misuse and overdose deaths. Postop, postoperative.

Maryland), state and local governments (all 50 states have some form of opioid prescribing guidelines or restrictions, as do some cities), state medical boards, professional societies, health insurers, pharmacy benefit managers, pharmacies, and local hospitals and healthcare systems.[45] Broad policies and targeted interventions to reduce opioid prescribing include improved medical student curricula; compulsory provider education; electronic medical record systems defaults, warnings, and limits; prescription drug monitoring programs; naloxone access laws; pain clinic laws; and stringent numerical restrictions on opioid prescribing.[31,77]

There are clear pitfalls of bowing to pressures that would result in seemingly attractive and expedient but ill-advised one-size-fits-all solutions. Many of these are outlined in the National Academies of Sciences, Engineering, and Medicine (Washington, D.C.) report "Pain management for people with serious illness in the context of the opioid use disorder epidemic."[78] Overall, the nation's response to the oral opioid crisis has been to tighten patient supplies and impose institutional and practitioner quality indicators based on pill counts. Governments, payers, and pharmacies have assumed authority for limiting opioid prescribing, often in indiscriminate ways, based on misinterpretation of Centers for Disease Control guidelines or based on no real guidance at all.[79] Pill counts have become *de facto* standards employed by healthcare organizations to highlight their success in reducing opioid use, yet there is no discussion of how those reductions are affecting patient outcomes.[78] One crucial problem is that agencies mandating policy restrictions do not measure, nor are they accountable for, patient outcomes.[78] Mandated opioid prescribing limits may be too low to adequately control pain, or too high to reduce oversupply.[80]

Another crucial problem is that supply-side restrictions focus on intermediate outcomes while ignoring patient-centric and population health outcomes. Intermediate outcomes include prescription pill counts, amounts of opioid used, number of unused pills left over, refill requests, opioid misuse, opioid diversion, health costs, and patterns of healthcare utilization (fig. 3). Patient-centric outcomes, arguably more important, include pain, adverse effects, function, recovery from illness, return to work or school, quality of life, morbidity, and mortality, and their implications for population health. Intermediate outcome statistics can also be misleading. For example, opioid prescriptions to opioid-naïve patients declined by 54% from 2012 to 2017,[32] and mean amounts (milligrams) prescribed per person decreased 13% from 2006 to 2017,[81] but average

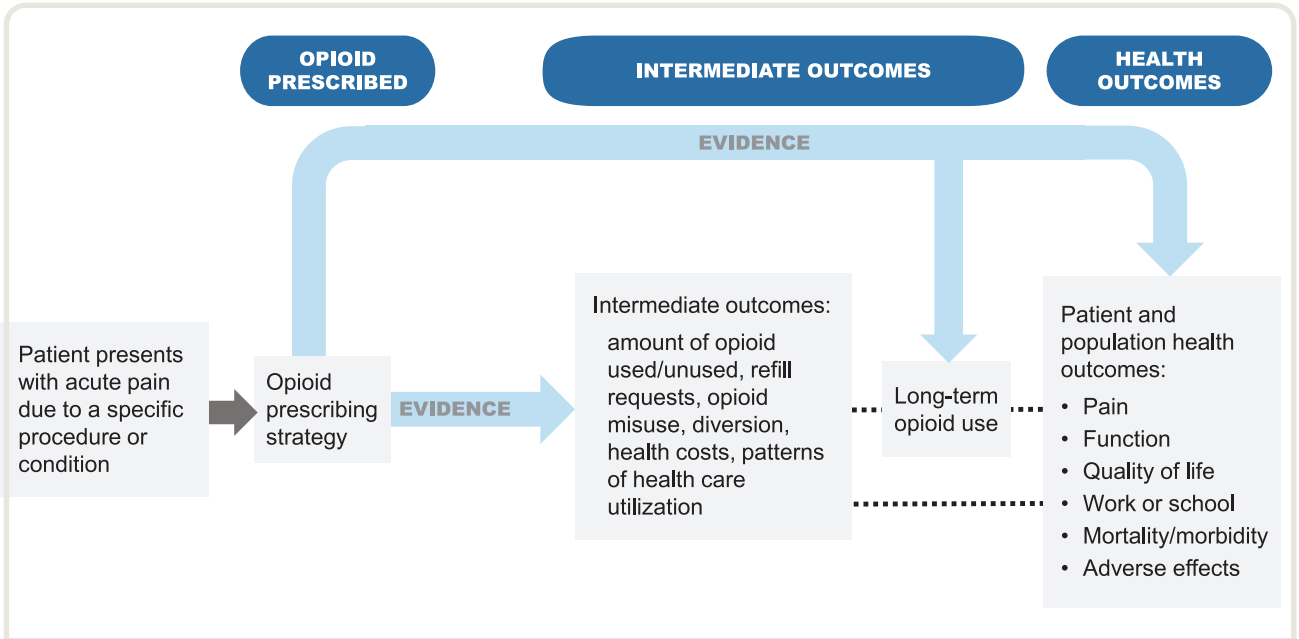

Fig. 3. Analytic framework for prescribing opioids for acute pain and evidence linkages necessary to support the development of clinical practice guidelines for opioid prescribing. The framework begins with the patient population with acute pain (*e.g.*, postoperative pain). The *wide arrow* indicates evidence evaluating the effects of an opioid prescribing strategy on a health or intermediate outcome. The *dotted lines* indicate linkages between different outcomes (*e.g.*, association between a lesser amount of opioid used and risk of long-term use or quality of life), not between an intervention and an outcome (or, in the case of intermediate outcomes and long-term opioid use, between one intermediate and another intermediate outcome). Short- and long-term health outcomes, both beneficial and harmful, may be seen at the patient and community or population levels. Reproduced from *Framing Opioid Prescribing Guidelines for Acute Pain: Developing the Evidence*[45] with permission of the National Academy of Sciences, courtesy of the National Academies Press, Washington, D.C.

prescription duration and the number of prescriptions for greater than 30 days both increased 38%.[81]

One example of opioid prescribing guidelines hyperfocused on supply-side restriction and their consequence is cancer, where pill count policies may adversely affect patient care. Opioid prescribing guidelines intended for noncancer populations are being inappropriately applied to cancer patients and cancer survivors, with concern about reduced access to effective pain management.[82] A recent survey of cancer patients and survivors found that one third were refused opioids by their physician, and one half were told that their pain treatment was limited by laws, guidelines, or insurance coverage.[82] The expressed fear was that while concerns about opioid misuse were certainly warranted, appropriate pain management was equally as critical.

Another focus of guidelines is on postoperative opioid prescribing, where calls for guidelines have been met with a plethora of recommendations by professional societies and healthcare institutions. Yet these are highly disparate (not surprising, given the above-described variability in interpatient pain experiences and analgesic responses). Among just one surgical type (abdominopelvic surgery), a recent review identified 15 clinical practice guidelines and 26 other pertinent documents containing 98 recommendations for discharge opioid prescribing, and there was substantial variability between them in the amount of recommended discharge opioid—even for the same procedure.[83] Moreover, in addition to the heterogeneity of the recommendations, only a tiny fraction (11%) of recommended interventions were supported by an assessment of strength or level of evidence.[83] Beyond surgery more broadly, there is prescribing variability within many other specific indications, by geographic region, provider type, provider, hospital, and within and between patient populations.[45]

Despite well-established interpatient variability in pain and recovery trajectories, several studies have attempted to identify the one right number of opioid pills needed by all patients postoperatively, with the goal of identifying the one right amount to prescribe.[84–86] Less stringent individualized approaches, such as those based on predischarge in-hospital opioid use, may be more successful,[85,87] but they are only applicable to hospital inpatients, and not more broadly to ambulatory surgery and emergency department visits. Numerable publications have rightly recognized the need to reduce excessive postsurgical opioid prescribing and promoted various approaches. Recent examples of local success in reducing postsurgical opioid pills counts are very promising.[88–91] However, patient effects beyond this intermediate outcome are yet unknown. Enhanced recovery after surgery protocols that promote opioid-sparing if not

opioid-free anesthesia have become widely implemented.[92] Nevertheless, such protocols did not affect discharge opioid prescribing.[93] Some reductions in opioid amounts prescribed at discharge after surgery have even been associated with worse postoperative pain control.[86] Risks of inadequate pain control include increased morbidity, care costs, progression to chronic pain and opioid use, delayed recovery, physical and emotional distress, and impaired physical functioning, daily activities, sleep, and return to work or school.[45]

Protocols that aim to "right-size" opioid prescribing in order to narrow the gap between opioid prescribing and amount used and thus reduce "leftovers" to decrease the storage and disposal burden on patients are highly laudable, yet challenged by the problem of variability. Such protocols can represent tradeoffs between opioid prescribing, use, and inadequate pain relief, as limiting discharge prescriptions to the amounts sufficient for the majority of patients means that some will have inadequate pain control.[45,94] Currently, one-size-fits-all opioid prescribing epitomizes the dynamic tension between protocolized and individualized medicine.[95]

In addition, the opioid supply chain now has two parts—the one the healthcare system controls, and a larger portion used for abuse that is illicit at its source. Decades ago this situation was the reverse, with most abused opioids originating in our medical supply. Restricting access with ill-considered policies may take pills from people who need them while leaving intact the main supply lines of the opioid crisis—primarily illicit fentanyl.

It is now recognized that supply-side approaches alone are not succeeding. Broad prescribing restrictions may be suboptimally effective because nearly half of all opioid doses and one quarter of all opioid prescriptions are accounted for by only 1% of providers.[77] In contrast, among the remaining 99% of providers, more than 85% of prescriptions were for less than the Centers for Disease Control recommendation of 50 mg morphine equivalents per day.[77] Since only a tiny fraction of providers account disproportionately for overprescribing, while most prescriptions written by the majority appear more appropriate, further broad increases in prescribing restrictions and more rigid dosing thresholds are considered unlikely to be beneficial, and more likely to reduce appropriate than inappropriate opioid use.[77]

In the realm of acute pain, restrictive opioid prescribing limits have not substantially reduced actual opioid prescribing, nor have they been the primary driver for the overall downward trend in opioid prescribing in the United States that has occurred over the last decade.[96] Greater restrictions on opioid prescribing are thought unlikely to be effective—and certainly not without the risk of inadequate pain treatment.[96] Moreover, sudden and/or involuntary discontinuation of chronic opioid therapy for pain due to clinician decision or supply restriction is not without potential consequence, such as withdrawal, increased or uncontrolled pain, psychologic distress, increased risk of suicidal ideation, opioid-related adverse events, and overdose death (particularly illicit opioids)—the very things we are trying to prevent.[86,97–101]

Legislative, regulatory, and insurer limitations on opioid prescribing alone have not met their intended goals and are considered unlikely to achieve them. One reason is that they impose tight restrictions on an extremely heterogeneous patient population.[78,80] Moreover, they focus more on intermediate outcomes, which are easily quantifiable but less important than the health outcomes that are more important to patients and population health (fig. 3).[45,102] Since the publication of the Centers for Disease Control guidelines with strict thresholds for opioid prescribing, enthusiasm has waned for such supply-side management in some quarters. The American Medical Association (Chicago, Illinois), in its essay "8 keys to end the nation's drug-overdose epidemic," suggests eliminating ineffective opioid prescribing restrictions and shifting focus to the illicit opioid overdose epidemic.[103] Even the authors of the Centers for Disease Control opioid prescribing guidelines have expressed dismay at the misapplication of their guidance.[104] While supply-side opioid policy has stayed or reduced prescription opioid misuse and associated overdose deaths, it appears to have had the unintended consequence of motivating opioid users to switch to illicit drugs and the associated consequence of increased overdose and death (fig. 1).[31,105]

It is clear that patients could benefit from better-informed practices and education regarding pain, oral opioid prescribing, and oral opioid use, and from a reduction in excessive overall and posthospital opioid prescribing. However, supply-side restriction alone is confounded by the problem of variability, and appears neither fully effective nor optimal, and further restrictions risk greater patient pain.

Demand-side Opioid Management

Demand-side (patient need) reduction in the opioid pool offers a more promising path forward if properly executed—that is, reducing pain and the need for opioids.[105] From the perspective of acute postoperative pain, the majority of patients (80%) report that their pain was not adequately managed.[46,106–108] Acute surgical pain not only causes suffering and diminished patient satisfaction[109,110] but also is associated with postoperative surgical complications (*i.e.*, surgical site and urinary tract infections),[43,111,112] and even engenders regret for having had surgery.[110] The problem of chronic postoperative pain affects up to 80% of patients,[113–115] and may lead to persistent postoperative opioid use.[102,116–118] Postoperatively, "one-third of adults receiving long-term opioid therapy report that their first opioid prescription came from a surgeon, indicating that postsurgical prescribing is important…in the opioid epidemic,"[119] and this is cited to suggest that opioids *per se* are the sole culprit. However, this ignores the fact that all chronic

postoperative pain started as acute postoperative pain, and acute postoperative pain was the reason for this one third of patients to be prescribed opioids in the first place. It is well-established that in opioid-naïve patients, acute postoperative pain is the greatest risk factor for chronic postsurgical pain.[120] Moreover, chronic pain is not limited to surgical patients. The incidence of new chronic pain in 1,840 1-yr survivors of critical illness (requiring intensive care unit care) was 18%,[121] and a systematic review of nine studies including 1,755 patients reported a 28 to 77% incidence of persistent pain after intensive care.[122] Neither found any difference between medical *versus* surgical patients in the incidence of persistent pain.

The target of greatest potential influence on the need for postoperative opioids is reducing acute perioperative pain and the potential consequence of transition to chronic postoperative pain.[115,120,123,124] As summarized recently, current therapeutic modalities such as multimodal analgesia, epidural analgesia, peripheral nerve blocks, perioperative gabapentinoids, intravenous ketamine, and intravenous lidocaine, while often effective in the immediate perioperative period, do not prevent chronic postoperative pain and/or persistent postoperative opioid use.[124–128] While pharmacologic innovations await, care model innovations may hold promise, such as the transitional pain service to provide continuity of pain care, education, and management to complicated patients after hospital discharge.[129–132] It is imperative to find more successful methods and practices than currently available, and this unmet need should be a pressing research focus.[95,102,124,133]

In the immediate, anesthesiologists should focus on carefully tailoring perioperative therapeutic regimens to the needs and circumstances of individual patients, and with the longest lasting benefit, preferably beyond just the immediate perioperative period and their time in hospital. If the prescribing of postoperative oral take-home opioids is to be right-sized, patients must feel confident that they will receive an adequate take-home supply to treat their pain and must receive the amount prescribed, and surgical prescribers must feel confident that they are providing enough to assure adequate analgesia and patient satisfaction, to minimize unwanted calls by patients for more, and to minimize the amount of unused leftover opioid pills. It has been recommended that perioperative initiatives focus more on reducing pain than on just reducing opioids *per se*.[95]

Pool-size Opioid Management

Last, and least illuminated or pursued, is the objective of shrinking the pool of opioids present in the community, to prevent diversion and misuse. Shrinking the opioid pool represents an unfulfilled opportunity for public health benefit at scale. The pool size depends not only on supply (inflow) but also on outflow, with the latter determined by voluntary disposal and take-back of unused and leftover opioids. The size of the opioid pool has major implications for potential misuse and adverse events. For example, among U.S. adults (older than 12 yr) who misused prescription pain relievers in 2019, 51% received them from a friend or relative (the pool), compared with 37% by prescription from a healthcare provider.[38]

Most patients with unused opioids plan to keep them for potential future need.[60] People keep unused medications because (1) it takes effort to discard them but no effort to leave them where they are, and (2) a natural inclination is to keep something that might be useful later on, such as a drug that once served a purpose (pain relief) and might do so again, particularly if future procurement is uncertain, inconvenient, or expensive.[134] Indeed, the most common reason for patients to retain unused opioids is to have them available should they need to treat pain in the future—theirs or that of others.[74,135] Among U.S. adults (older than 12 yr) who misused prescription pain relievers in 2019, the vast majority (66%) did so to relieve physical pain.[39] This again highlights the importance of the problem of undertreated pain, well-recognized in adults,[20] and more recently in children.[136] Among adults who kept unused opioids and then shared them (one of the definitions of misuse), 73% did so to help another person manage their pain.[58] Hence a major motivation for retaining unused opioids, and a barrier to shrinking the opioid pool, is patients' fear of pain and of their inability to receive proper future treatment. Another major reason patients retain unused opioids is the barriers to disposing or returning them.

Compared with the unremitting focus on restricting opioid prescribing, opioid disposal and return (take-back) have received scant attention. Patient storage of unused medications, lack of return, and lack of education by healthcare providers about disposal have remained unchanged for more than a decade, even in the face of the opioid crisis.[137] Patient education about opioid disposal has been called staggeringly low.[135]

Prescription Opioid Ecosystem

A new paradigm and new messages are needed. Our proposal is the concept of the prescription opioid ecosystem (fig. 2). The ecosystem consists of providers/prescribers, pharmacies, patients, and disposal (and manufacturers, distributers, and pharmacy benefit managers, albeit not discussed here), all of which bear directly on the opioid pool.

The prescription opioid ecosystem is a superset of the recently introduced concept of opioid stewardship.[138] Opioid stewardship is modeled on now-standard institutional antibiotic stewardship programs. One definition of opioid stewardship is "coordinated interventions designed to improve, monitor, and evaluate the use of opioids in order to support and protect human health."[139] The opioid stewardship concept has also been echoed by the National Quality Forum (Washington, D.C.).[140] Nevertheless, this important yet still developing concept lacks consensus

definition and implementation, and is sometimes conflated with institutional administrative superstructures or with clinical pain management approaches.[141–144] In addition, opioid stewardship programs are institution-based and institution-specific, often focused mainly on prescribing practices, prescribing monitoring, and addiction.[141–144] Programs are often linked to hospital pharmacy consult services or to clinical pharmacy specialists within hospitals and health systems. Last, they are not widely found, and are variably effective.[141–144] Programs focus on clinicians, administrators, quality assessment personnel, clinical disciplines, administrative structure, organizational policies, tasks, tracking, and reporting.[138,142,145] These are all extremely valuable institutional efforts, but they are not patient-centric, and do not directly address patients and communities at large or the problem of the opioid pool and its consequences. The prescription opioid ecosystem can include institution-based opioid stewardship, but extends well beyond, to the broader concept of opioid use, storage, return, and harm reduction, with a specific focus on patients and communities.

Prescription opioid ecosystem patient messaging and implementation should be patient-centric and stress safe handling and storage of opioids, opioid use only by the recipient and only for the prescribed indication, patient transition to nonopioid analgesics as recovery progresses, and then appropriate opioid return or disposal to minimize diversion, misuse, and harm. One suggestion is the novel messaging that opioids are not "given" to patients (denoting permanent possession) but rather "loaned" for appropriate and recipient use only, and that they should be returned when no longer needed. The healthcare system needs to make "the right to return" as easy or easier than "the right to receive." Inherent in this strategy, however, it is crucial that patients need to be confident and assured that their next episode of pain will be appropriately treated, lest they hoard unused opioids for fear that any such future pain and suffering will not be treated.

Opioid ecosystem education should target greater patient (and caregivers of children) engagement in pain management and safe opioid use.[146] Patient education by providers and other caregivers is unquestionably needed and an attractive opportunity for shrinking the opioid pool. However, surveys of U.S. adults found that 40 to 50% said they received no information on either safe storage or proper disposal.[58,147] Another survey of children's caregivers found that education on proper storage was reported by only 60%, and education on disposal by 50%.[66] Opioid disposal rates are typically less than half the rate of patient education.

Opioid education is laudatory and unassailable as an ideal. Preoperative education may reduce postoperative pain scores and opioid use,[148] or hasten opioid cessation.[149] Nevertheless, it must be recognized that patient education alone is insufficient and inconsistent, effective strategies are lacking, little progress has been made, and education will require substantial effort, take considerable time, and need greater evidence of effectiveness.[150] Passive education (informational pages and brochures) has unfortunately not been successful. A single-page document given to patients after dental surgery increased the proportion of patients who disposed or reported intent to dispose of unused opioids by only 22%.[68] Dissemination of an educational brochure about safe disposal of unused opioids doubled the disposal rate, but still only a small fraction (22%) of patients did so.[151] More recently, even with greater awareness of the opioid crisis, patient education handouts did not increase opioid disposal.[152,153] Although education of children's caregivers on proper storage and disposal was reported by 60% and 50%, respectively, locked storage and disposal were reported by only 18% and 25%.[66] Moreover, there is insufficient knowledge among those providers who would need to be the educators. In an opioid knowledge assessment examination taken by physicians, nurses, and pharmacists involved in opioid administration in Pennsylvania hospitals, only 9% of respondents correctly answered all of the 11 basic questions.[154]

Appropriate, rational, and safe opioid prescribing as well as safe return or disposal need to be part of undergraduate and graduate medical and pharmacy curricula and continuing medical and pharmacy education. Educating patients cannot occur until we educate the educators. From the perspective of postsurgical opioids, preoperative clinics, or possibly transitional pain services, typically run by anesthesiologists, could be the most opportune place for perioperative practitioner and surgical patient education about postoperative pain, opioids and other pain drugs, opioid stewardship, and opioid return/disposal. More broadly, primary care providers, who are the largest group of opioid prescribers,[67] constitute the greatest need and opportunity for provider, and in turn, patient education.

Other approaches to the prescription opioid ecosystem are also needed that target disposal and return more specifically. Home disposal is one option. Unfortunately, home disposal guidelines for patients vary widely, can be confusing, are infrequently communicated, and are not intuitively found by patients. Contrasting recommendations, even within and between U.S. federal and state agencies (Drug Enforcement Administration; Environmental Protection Agency, Washington., D.C.; state boards of pharmacy; individual state agencies) can be confusing to patients.[155] The U.S. Food and Drug Administration (Silver Spring, Maryland) recommends flushing some drugs down the sink or toilet, while recommending that others should be mixed with used coffee grounds, dirt, or cat litter, placed in a closed unmarked container, and thrown in the garbage.[156] In contrast, the U.S. Environmental Protection Agency advises against flushing unwanted drugs down the toilet. U.S. news media articles rarely cover flushing as an option, and often present it as environmentally harmful.[155] Some state guidelines contradict federal guidelines.[157,158]

In contrast to the United States, Health Canada (Ottawa, Canada) recommends that unused drugs be returned to local pharmacies or municipal waste disposal centers and discourages other forms of disposal (flushing, pouring down the drain, or throwing in the trash).[159]

The current difficulty of returning prescription opioids contrasts markedly with the ease of obtaining them. This is illogical and unsafe. A less confusing, more effective, and more environmentally sound approach is needed, specifically the creation and facilitation of effortless and free pathways for disposal and return that are widely known, widely available, and widely used. Events such as National Prescription Drug Take Back Day are welcome, but occur only once per year, and in a limited 4-h window,[160] and are not widely publicized and well-known.[161] These do collect tons of unused medications, but only a tiny fraction are opioids,[162] and take-back events and drug disposal sites remove only a miniscule fraction (0.3%) of opioids dispensed.[163] This is inadequate. More promising are year-round drug disposal locations, yet the availability, awareness, and use of these sites, particularly for opioids, is insufficient.[164] Most patients (84%) surveyed would be more likely to use a take-back kiosk if it was in a frequently visited location.[135] Even though there is considerable variability in opioid prescribing, the variability in opioid consumption and thus the variability in amounts left over are even greater.[47] Hence intervention on the disposal side may have even better impact than just trying to throttle opioid dispensing.

There need to be common sense, convenient, widely available, accessible, appealing, and inexpensive (preferably free) methods for patients to return unused opioids. Even terminology may be influential. "Return," "take-back," and "give-back" may have subtle influence on behaviors, as the former two terms connote effort required on the part of patients and potential inconvenience, while the latter does not and may even sound more genial. One approach is mailable disposal bags. Providing patients with a bag containing an inactivating modality (*e.g.*, activated charcoal, coffee grounds) for in-home opioid disposal was found in various studies to double the disposal rate compared with an educational pamphlet (57% *vs.* 29%),[152] increase it by 50% (33% *vs.* 19%),[75] increase it by 20%,[165] or have no effect at all.[153] An interactive Web-based educational program combined with a disposal kit was more effective than just a kit alone.[75] After pediatric surgery, provision of a mail-back envelope resulted in opioid return by 19% of patents, comprising 58% of the prescriptions written.[166] Opioid "buy-back" sounds even more appealing, and may also facilitate return.[91] This novel pilot program for buy-back of postsurgical opioids (nominal $5 reimbursement with a limit of $50) resulted in 30% participation of 934 patients, returning 3,165 unused pills (median 10 per patients, 22% of pills dispensed), at a cost of $31 per patient. In a patient survey, most (70%) reported that compensation would lead them to dispose of unused opioids.[135]

Regulations require that prescription drugs must be dispensed with patient instructions for use, and there are telephone numbers for refills on every medication container label for patient convenience, refills, and obvious business reasons. Perhaps regulations are also needed requiring that opioids be dispensed with explicit and plain instructions for proper return or disposal, and preferably with some message on the label rather than just a handout. Perhaps patient instructions, including addresses/telephone numbers of disposal stations, and a return mailing envelope for unused drugs, should be mandatory. Such an envelope should be preaddressed and postage-prepaid, to maximize return rates. More than half of patients surveyed would use such a prepaid envelope for opioid return.[135] Regulations must be federal, for uniformity, lest there be a patchwork of variable state regulations. Opioid take-back is currently subject to federal, state, and board of pharmacy regulations, which may be complex if not conflicting and certainly confusing to patients.

Practicum

What can anesthesiologists and acute pain practitioners do, ideally together in concert with surgeons, to implement these ideas about the prescription opioid ecosystem, particularly as they apply to perioperative care? Actionable opportunities include both advocacy to improve federal opioid policy and focused perioperative care.

Prescription Opioid Policy

More informed, thoughtful, and proactive opioid policies, and better understanding of their successes and failings, are one immediate opportunity, and should be enthusiastically advocated by practitioners. Research on federal and state opioid policy has predominantly focused on state prescription drug–monitoring programs, prescribing policies, federal regulations, treatment access, and pain clinic laws.[167] Research on effectiveness examines proximal outcomes (effect of prescription drug monitoring programs on prescribing, effect of treatment access policies on treatment utilization), but not distal outcomes (patient and population health) and unintended consequences. Increasing complexity of the policy landscape has also been identified, with heterogeneity resulting in variable effectiveness, and the need for better methodologic rigor has also been identified.[167] Revision of less effective and promulgation of more effective policies should be imperative, but is likely to be slow.

There is one novel policy approach offering remarkable potential benefit. Ideally it should be immediately available to acute pain practitioners and to surgeons prescribing postdischarge opioids. It affects the supply side of the opioid ecosystem. A new federal law, which permits partial fills of oral opioid prescriptions, particularly useful for acute and postsurgical pain, represents a substantial opportunity and underused ecosystem approach for reducing the opioid pool. This law, enacted in 2016, allows partial filling of schedule II opioid

Box 1: Partial Filling of Opioid Prescriptions

1. Partial filling of prescriptions for schedule III, IV, or V controlled substances. This is currently permitted (21 CFR Part 1306.23), provided that the total quantity dispensed in all partial fillings does not exceed the total quantity prescribed, no dispensing occurs later than 6 months after the initial prescription, and each partial filling is properly recorded.
2. Partial filling of prescriptions for schedule II controlled substances. The Comprehensive Addiction and Recovery Act of 2016 amended the Controlled Substances Act (21 U.S.C. 829, new paragraph f) to allow partial filling of prescriptions for schedule II controlled substances when requested by a patient or practitioner. Additional requirements are that partial filling is not prohibited by state law, the total quantity dispensed in all partial fillings does not exceed the total quantity prescribed, and no dispensing occurs later than 30 days after the initial prescription (unless it was an emergency oral prescription, in which case the remaining portion must be filled within 72 h).

   In December 2020, the Drug Enforcement Administration issued a Notice of Proposed Rulemaking (Docket No. DEA–469) to modify the Code of Federal Regulations (21 CFR Part 1306) to revise the Drug Enforcement Administration regulations to incorporate the new statutory provisions.[168]

   Where a practitioner requests that a schedule II prescription be partially filled (as the Comprehensive Addiction and Recovery Act now allows), the proposed rule states that the face of the written prescription must specify the quantity to be dispensed in the partial filling.

   Where a patient requests that a schedule II prescription be partially filled (as the Comprehensive Addiction and Recovery Act now allows), the proposed rule states that the pharmacy would be required to indicate on the prescription that the patient requested the partial fill. One caveat is that where a practitioner has requested the partial filling of a prescription, the patient may not request a partial filling in an amount greater than that specified by the practitioner. A patient request to the pharmacy for a partial fill would not require the consent of, or notification of, the prescribing practitioner.

   In addition, the Drug Enforcement Administration recognized that many postsurgery patients may have a difficult time visiting a pharmacy in person; therefore, the proposed rule would not require an in-person request by the patient in every case and would allow alternative pathways for the patient to make such a request and specify the amount to be filled (*e.g.*, phone call by the patient to the pharmacist, or a signed written note from the patient and delivered by a family member to the pharmacist).

prescriptions when requested either by a patient or practitioner. Partial filling of prescriptions for schedule III to V drugs was already allowed (box 1).[24] Partial fills afford potential benefit to patients and society *via* regulatory flexibility, reduction of opioid overuse and dependence, a diminished amount of unused opioids available for misuse or diversion, and reduction of healthcare expenditures, while meeting the needs of those patients with ongoing pain who require opioids.[24] Importantly, a patient request to the pharmacy for a partial fill would not require the consent of, or notification of, the prescribing practitioner, would not require additional consent, and would not impose dispensing delays, thereby mitigating burdens to pharmacies, practitioners, and patients. This gives patients the choice and is patient-centric. It is estimated that 36 million postsurgical prescriptions annually could be partially filled.[24] A survey found that about half of patients would likely select partial opioid fills, but concerns did exist about future availability if needed, inconvenience of returning to the pharmacy, and additional dispensing copay.[135] Assuming a typical postsurgical prescription of 30 pills, and that postoperative patients consume only 33% of prescribed medication (according to one study[151]), this leaves 723,600,000 pills unused annually. If only half of the 36 million postsurgical prescriptions were partially filled, this would reduce unused leftover opioids and the annual opioid pool by 540,000,000 pills, and accrue more than $656 million annually in cost savings from reduced dispensing and an additional $3 million in disposal costs.[24] Success of this endeavor, however, will rest primarily on prescribers, because patients may be unlikely to request a partial fill.[24] Success will also require seamless no-questions-asked, no-charge fills of the unfilled prescription by pharmacies. Completing partial fills will have a cost to pharmacists, but this is estimated at less than $15.[24] This cost should not be borne by patients. Of note, the National Association of Chain Drug Stores (Arlington, Virginia) has endorsed the partial fill concept.[169] The small cost of partial opioid fills pales in comparison to the cost savings from pills dispensed, reduced leftover opioids, shrunken opioid pool, potential for diminished opioid misuse, addiction, and diversion, and improved public health. Federal law, which enabled partial opioid fills, was enacted in 2016. This needs prompt implementation. Partial opioid fills could be the single most effective intervention to deplete America's medicine cabinets of unused prescription opioid pills, shrink the opioid pool, improve the prescription opioid ecosystem, and prevent misuse, diversion, and death.

In addition, there may be other stakeholders and influences outside the clinical milieu that influence the opioid ecosystem. For example, to what extent do protocols of the U.S. Department of Justice (Washington, D.C.) and Department of Homeland Security (Washington, D.C.) influence providers' abilities to prescribe medically necessary amounts of opioids? The Homeland Security Web site focuses primarily on stopping the flow of illicit opioids and supply reduction.[170] While it also states that "demand reduction is a critical element in the U.S. government's comprehensive efforts to combat opioid abuse," nothing follows. Similarly, the White House Office of National Drug Control Policy (Washington, D.C.) announcement of 2021 policy priorities appropriately emphasizes opioid use disorder treatment, access and workforce issues, and illicit supply reduction.[171] Perhaps the opioid ecosystem concept and enhanced opioid disposal and return can be brought to the attention of Homeland Security and the Office of National Drug Control Policy and embraced as part of the countermeasures strategy.

Opioid Practice

Immediate actions include the education of patients; anesthesia and surgery colleagues and institutions (this is generally not being adequately taught in medical school, residences,

Box 2: Perioperative Practitioner Engagement in the Prescription Opioid Ecosystem

Anesthesiologists and surgeons engage multiple facets of the perioperative opioid ecosystem. Anesthesiologists can have prominent roles in each step or even comprehensively oversee the process. Postoperative opioid needs (demand) can be diminished by optimized intraoperative/postanesthesia care unit (PACU) anesthesia care, opioid supply can be more carefully managed, consumption can be reduced by education about expectations and alternatives, and opioid stewardship can be enhanced by education about storage, disposal, and return.

1. Educate patients pre- and postoperatively on pain, pain management, and opioid use

   Establishment of a therapeutic alliance between patients, anesthesiologists, and surgeons is needed, with clear expectation as to who will provide the needed education. Perioperative education is often completely missing, but even when present may inadequately set expectations for pain relief, incompletely outline the use of opioids as one tool among many to control pain, and fail to review risks and proper handling of leftover opioids.[150] Educational materials are immediately and publicly available (*c.f.*, "Safe and Effective Pain Control after Surgery" from the American College of Surgeons, Chicago, Illinois[174]; and "Opioids and Pain Management" from the Michigan Opioid Prescribing Engagement Network, Ann Arbor, Michigan[175]). Preoperative education may reduce postoperative pain scores and opioid use,[148] or hasten opioid cessation.[149] Patient education supervised by anesthesiologists should be a key component of a comprehensive perioperative opioid use and risk reduction strategy.[176]

2. Educate patients pre- and postoperatively on opioid stewardship, storage, and disposal

   Preoperative anesthesia assessments, discharge planning, and outpatient PACU and inpatient ward discharge visits afford opportunities to educate patients and caregivers whose focus is undistracted and attuned. Topics should include pain expectations, opioid and nonopioid analgesics and optimal use, avoidance of dangerous opioid drug interactions, proper storage of unused opioids, the idea that opioids are "loaned," not "given," and the need for proper disposal or return ("give-back") and the responsible and effective methods for doing so, as well as the benefit to them and society. There is also the need to educate the educators.

3. Evaluate patient preoperative opioid use

   Consider preoperative opioid tapering for patients on chronic opioids. Chronic preoperative opioid use is common[177] and a risk factor for worse surgical outcomes, surgical complications, poor pain control, greater suffering, opioid-related respiratory depression, perioperative dose escalation and prolonged postoperative opioid use, longer length of stay, greater costs, more frequent readmissions, and more difficult to control postoperative pain.[178,179] Tapering preoperative opioids has been suggested, with less acute and chronic postoperative pain and opioid consumption and enhanced functional recoveries among the hoped-for outcomes.[178] Unfortunately, it is simply not known for whom and to what degree preoperative opioid taper is appropriate. There is limited evidence for the effectiveness of tapering, and there are few successfully proven protocols.[178] Recent evidence suggested that reducing opioid use preoperatively did not result in lower postoperative opioid use.[179] In addition, there may be risks. Opioid discontinuation, whether abrupt or with dose reduction, significantly increased risk of suicide (hazard ratio 4 to 5), and patients with abrupt discontinuation were more likely than others to overdose on heroin (*vs.* prescription opioids).[101] Discontinuation of long-term opioids was associated with a threefold greater risk of overdose death.[98] Shorter time to discontinuation was associated with greater risk of opioid-related adverse events.[99]

   Identify patients with opioid use disorder. First consideration should be given to stabilizing patients by referral for medication-assisted treatment, counseling, support, and other evidence-based interventions. Undertreatment of opioid use disorder, inadequate availability of treatment, and underutilization of and access to medication-assisted therapies such as methadone and particularly buprenorphine are well-known. Those having more urgent surgery should have opioid use gauged and surgical and anesthesia teams notified in order to optimize care. Patients on medication-assisted treatment will require that to be managed, generally with continuation throughout the perioperative period (definitely methadone, although buprenorphine is more controversial and with limited evidence).[180,181] Discontinuation of medication-assisted treatment may confer critical risks of return to illicit drug use or overdose.[182]

4. Implement evidence-based anesthesia that confers benefit and reduces risk

   Use patient-specific intraoperative and PACU anesthetic regimens that provide excellent perioperative pain relief, optimize patient recovery trajectory, minimize postdischarge pain and opioid requirements, and ideally confer continued and long-term benefit after discharge.[59] Remember that the majority (80%) of surgical patients report inadequate pain treatment,[46,106–108] acute surgical pain causes suffering, diminished patient satisfaction, and is associated with surgical complications and regret,[43,109–112] and is a major risk factor for chronic postoperative pain and persistent postoperative opioid use.[102,113–118] Opioids are the most efficacious systemic analgesics available for moderate to severe pain. Multimodal approaches may have benefit and spare opioids when evidence based. Choose strategies that maximize pain control while minimizing the need for postoperative discharge oral opioids and associated potential long-term harm.[102] Adequate analgesia, not withholding needed opioids, should be the primary goal.[133] Opioid-sparing by itself is not likely meaningful to patients unless accompanied by improved patient-centric outcomes like better pain relief or the sparing of undesirable opioid-related side effects.[183] Opioid-free anesthesia has not been shown to have benefits beyond opioid-sparing strategies, to influence or prevent persistent postoperative opioid use, or to prevent postoperative opioid overprescription.[92,95] Regional anesthesia and other nonopioid multimodal strategies generally reduce postoperative pain opioid requirements for several hours to days; catheter-based systems can extend benefits of some blocks for a week or more. Newer techniques of percutaneous neuromodulation may be promising.[184] Current approaches need improvement. Multimodal analgesia decreases acute but not chronic postoperative pain.[123] Epidural anesthesia may not protect against persistent opioid use.[125] Nerve block for total knee or shoulder arthroplasty did not decrease persistent postoperative opioid use,[126,127] and perioperative gabapentinoids have no effect on chronic postoperative pain.[128] Intraoperative methadone, with or without ketamine, for some inpatient and outpatient procedures, can result in less postoperative pain and opioid use, with benefits that last for weeks to months.[185–189]

5. Right-size postdischarge oral opioid prescriptions

   Postoperative patients should ubiquitously receive nonopioid analgesics but may experience moderate to severe pain needing opioids. Adequate postoperative pain treatment is imperative, and fundamental for preventing conversion from acute to chronic pain.[115] Opioid-sparing and multimodal techniques may reduce immediate perioperative opioid needs, but little patient benefit accrues if discharge opioid amounts are not tailored, and particularly if under- or overprescribed. Withholding needed opioids is not appropriate. Interindividual variability in pain severity and duration and analgesic response confounds one-size-fits-all postdischarge oral opioid prescribing. Communication with surgical teams about appropriate discharge opioids while adding nonopioid analgesics, taking responsibility where possible for designing and implementing opioid-sparing discharge analgesic plans, and arranging transitional pain management care are all responsibilities anesthesia groups and acute pain services might assume. Commensurate with responsibility for proper opioid prescribing is patient education about opioid stewardship, safe use, storage, disposal, and return of unused opioids.

6. Consider implementing transitional pain management

   This addresses the period between discharge and the re-establishment of care with the patient's primary provider for patient care and education about postoperative pain, opioids and other pain drugs, opioid stewardship, and opioid return/disposal. The first transitional pain service was developed to reduce chronic postsurgical pain by identifying high-risk patients and providing coordinated and comprehensive care from a multidisciplinary team of pain physicians, psychologists, physiotherapists, and advanced practice nurses.[129] Patients are seen preoperatively, postoperatively, or as outpatients for up to 6 months after surgery. A service can bypass potentially long waiting times for postoperative patients to be referred and seen in chronic pain clinics. Expanded aims are to reduce opioid consumption in preoperatively opioid-naïve and opioid-experienced patients.[130,131] Services may include opioid, nonopioid, and multimodal analgesia management to improve pain and opioid weaning, nonpharmacologic interventions including acupuncture and physiotherapy, and psychologic interventions around pain education and coping.[131] This may enhance communication between surgical team, primary providers, and chronic pain specialists, and is amenable to telehealth implementation.

and departments), on unmet needs for appropriate treatment of postoperative pain; appropriate, rational, optimal, and balanced use of opioids for postoperative pain, opioid stewardship, and opioid disposal/return; and the need for anesthesiologists to devise anesthetic and postoperative regimens for optimum pain relief, optimum recovery trajectory, and appropriate amounts of opioid prescribing and opioid use.[95,102,133,172,173] These are summarized in box 2 and figure 4.

How can the opioid ecosystem concept, shrinking the opioid pool, and improving opioid returns reduce opioid-related deaths, since most deaths result from illicit opioids? It is because prescription oral opioids are a gateway to the use of heroin and illicit fentanyl. The majority of U.S. heroin users also use prescription oral opioids,[38] and up to 80% of heroin-dependent individuals report initiating with prescription oral opioids.[25,190,191] Prescription opioid-dependent patients, faced with unavailability due to decreased provider prescribing and other supply-side reductions, abuse-deterrent reformulations, tamper-resistant pill dispensers, street market shortages, and high street costs, simply turned to cheaper and more accessible heroin as the unintended policy consequence.[18,35,105] Heroin became substitution therapy for prescription opioids. Fentanyl was subsequently introduced as an efficient supply-side market response to opioid demand, prescription opioid shortages, declining heroin purity, shortages, and "supply shocks," as well as lower production cost, easier distribution, and greater profitability of fentanyl *versus* heroin.[26,27] Moreover, illicit fentanyl is increasingly being sold deceptively as adulterated or fully counterfeit prescription opioid pills, such as oxycodone, or as heroin,[192] and also contaminates other illicit drugs such as cocaine and methamphetamine.[193] End-users often unknowingly consume illicit fentanyl, as neither they nor dealers know their drugs contain fentanyl, and overdose may result. Thus, user demand is for opioids, not illicit fentanyl *per se*, and the opioid supply chain just responded with fentanyl. Therefore, by reducing the size of the opioid pool, potential diversion, and misuse, the demand for prescription opioids to misuse can be slacked, as can the market substitution demand for heroin and illicit fentanyl, as well as their use and resulting overdose. While many opioid deaths have been caused by overdoses of street drugs (*e.g.*, fentanyl), not prescription opioids, it is considered inarguable that oral prescription opioids continue to play a prominent role in the opioid crisis.[194]

A caveat about shrinking the prescription opioid supply, particularly given the number of individuals with existing opioid use disorder, is that we not repeat past unintended consequences. Shrinking of the prescription opioid pool will need expansion of programs for medication-assisted therapy of opioid use disorder.

Conclusions

The opioid epidemic has not abated. The paradox is that opioid overdoses continue to escalate while opioid prescribing has decreased, despite the innumerable research publications documenting opioid prescribing and use, and the plethora of well-intentioned federal, state, local, and institutional legislation and policies, proliferation of guidelines, efforts by practitioners, and public awareness. More than half of dispensed

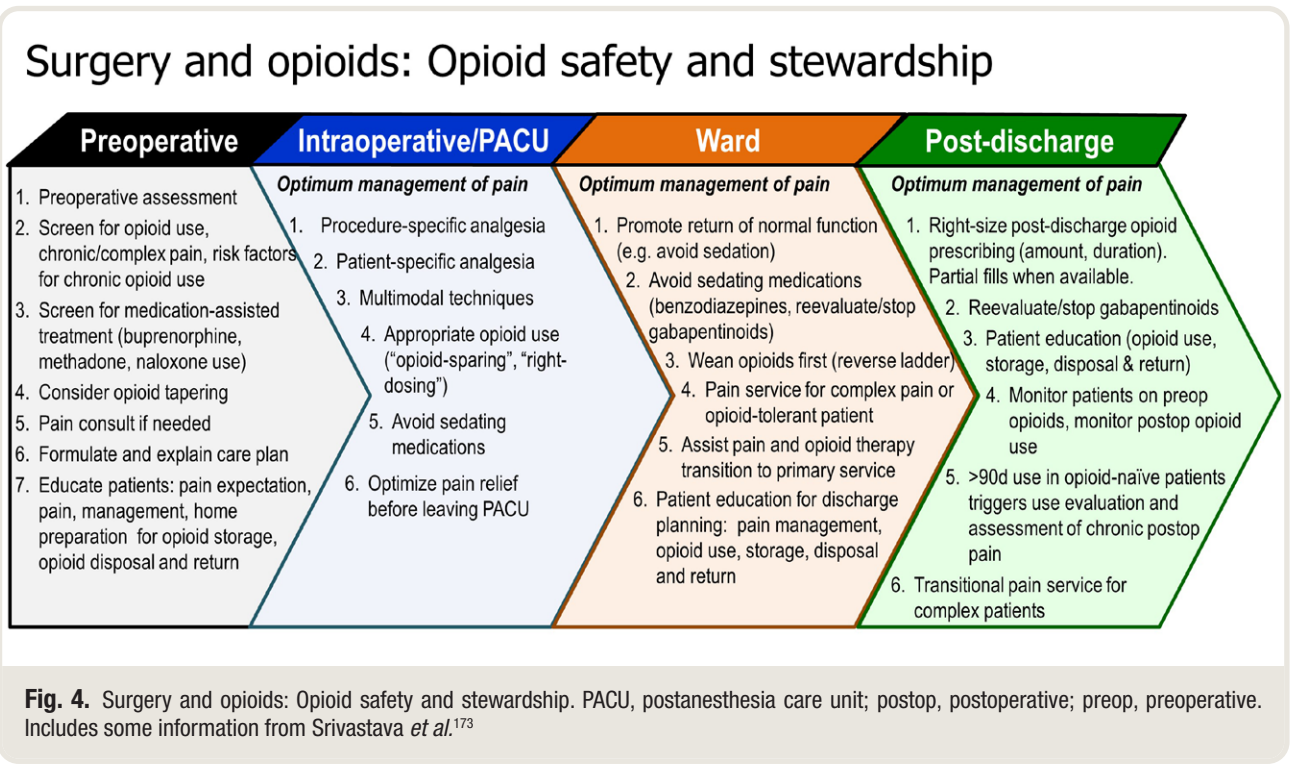

Fig. 4. Surgery and opioids: Opioid safety and stewardship. PACU, postanesthesia care unit; postop, postoperative; preop, preoperative. Includes some information from Srivastava *et al.*[173]

opioids in the United States are unused, and most are not stored appropriately, creating a prescription opioid pool susceptible to diversion, misuse, and addiction. Attempts to solve the problem by restricting patient supply alone have not succeeded, and the prescription opioid pool remains large. Additional novel efforts to shrink the pool are needed, both by diminishing demand (reducing pain through better treatment) and by facilitating opioid disposal and return. The prescription opioid ecosystem model encompasses these concepts, can be readily understood by providers and patients in a simple supply–demand paradigm, and highlights actionable policy and patient care opportunities.

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