Hudson Institute

Beyond Opioids in Medical Treatment:

Improving Patient Outcomes, Reducing Costs, and Serving Public Health with Comprehensive Pain Management

David W. Murray, Senior Fellow
& John P. Walters, Chief Operating Officer

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Report

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Hudson Institute
1201 Pennsylvania Avenue, N.W.
Suite 400
Washington, D.C. 20004

P: 202.974.2400
info@hudson.org
www.hudson.org

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Executive Summary

With a record 63,600 overdose deaths in 2016—the latest year for which there is comprehensive data—the United States is in the midst of the worst drug crisis in its history. While multiple nationwide efforts are underway to stem the damage, all indicators show the opioid crisis continuing to worsen. Effectively confronting this epidemic involves more than just assessing the toll and affixing responsibility. Rather, policy solutions must be provided that will reduce the human and social losses.

The following report provides an overview of recent developments in the opioid epidemic of use, dependency, and overdose deaths; identifies the two major pathways by which opioid initiation worsens into serious personal and social costs; and then reviews emerging policy changes that can serve to mitigate these costs, particularly with regard to the medical practice dimension of the epidemic.

The report contains five central arguments, showing where the crisis now stands and then addressing pathways along which remedies—some existing, some in development—could be provided. It then examines existing empirical support for alternative approaches, evaluates procedural and regulatory impediments to these alternatives, and calls for new models of medical practice and intervention that could alleviate the current opioid crisis.

Specifically, this report shows that:

1. With more than 42,000 overdose deaths attributed to opioids for the most recent year with complete data (2016), the toll, as found in preliminary reports for 2017, is still rising. The unprecedented surge in the availability of prescription opioids has been a major driver of opioid use consequences, particularly as excess pills contributed to non-medical "diversion" and may even have triggered a "cross-over" into the illicit market. At this stage of the epidemic, however, the illicit opioid black market, particularly for illegal synthetic opioid analogs smuggled internationally, is the most significant factor leading to overdose deaths.

   Prescription deaths have, as of 2016, declined somewhat, while heroin and (illicit) fentanyl-related deaths have risen steeply. The latest data available, found in a report in the *Journal of the American Medical Association* in May 2018, shows that among 42,249 opioid-related overdose deaths for 2016, 19,413 involved synthetic opioids, 17,087 involved prescription opioids, and 15,469 involved heroin.

   Nonetheless, reforming medical practice and pharmaceutical opioid availability remains a significant imperative. Finding better interventions for treating both chronic and acute pain, and moving the medical system "beyond opioids," appears as a new responsibility for medicine.

While a history of poly-drug abuse proves to be a critical risk factor for experiencing opioid dependency or overdose, for many Americans, such standard medical interventions as surgery represent a substantial pathway for opioid initiation, which not uncommonly leads to persistent opioid use and misuse.

Studies attest that for opioid-naive patients undergoing a variety of surgeries, a substantial fraction (some 6 to 9 percent) will persist in using the opioid prescription many weeks after surgery. In some instances, for patients already opioid-experienced, the proportion of persistent users as much as a year later can range from 45 percent to as high as 71 percent. Non-opioid alternatives are needed in medical practice to reduce opioid exposure beyond necessity.

2. Even under proper medical supervision, an extensive reliance on opioid medications for pain management presents several risks for patients, especially at high doses continued for long periods of time. These risks are present even in the absence of misuse or dependency. While the exact pathway from proper and supervised medical use of opioids to misuse is still poorly understood, evidence of surprisingly large numbers of unused or residual prescription opioids after a medical episode suggests that standard dispensing practice may be over-reliant on opioids when alternatives could supplement, or even supplant, their use.

   Overall, the two major pathways for opioid misuse—the illicit opioid black market and the unintended consequences of proper patient care—have in fact intersected in recent years, each feeding the other and providing sources of misuse as the crisis has grown. The flow of illicit narcotics across our borders must be shut down, but standard medical practice must also be reformed in order to stem the rising damage in a manner that will be comprehensive.

3. Progress has been made in one dimension of the effort to reform medical practice regarding opioids. Since a high point in prescribing in 2011, the number of opioid prescriptions, as well as the strength of dosage units, has begun to fall. By 2015, the Centers for Disease Control reported a more than 17 percent decline in pharmaceutical opioid dosages on a *per-capita* basis.

   The improvement has come through administrative action, guideline recommendations from health agencies, congressional pressure, and even proposed shifts in Drug Enforcement Administration production quotas for pharmaceutical manufacturers.

   But simply driving down access to medications, while important, cannot by itself be a sufficient response. Not only are patients with legitimate medical needs being pressured, some physicians also feel that their medical judgment is being circumscribed. What is needed is a solution to the other side of the equation, which is to provide non-opioid alternatives to patients who would otherwise be left with untreated serious pain.

4. New, multi-modal protocols and medications that incorporate developing as well as existing non-opioid analgesics show promise in surgery and in treating chronic and acute pain. While new drugs are being developed, it is important to note that, as Dr. Keith Humphreys stated in the *Washington Post*, "The problem in American medicine is not a lack of alternatives to opioids, but the minimal utilization of the many non-opioid treatments for pain that already exist."

   With these new multi-modal models, not only is exposure to opioids reduced substantially and overall circulation of unused opioids curtailed, but, equally important, patient outcomes are improved. Compared to the excessive patient and societal costs of opioid reliance, such superior protocols should result in improved patient flow and discharge, quicker recovery, fewer readmissions to the hospital, and reduced hospital costs.

   The long-term result will likely provide superior patient wellbeing and more effective medical practice. Additionally, the goals of reducing the opioid crisis will be provided for without the consequence of untreated pain.

   This report reviews multiple studies showing strong empirical evidence of non-opioid alternatives already being deployed successfully in the treatment of chronic and acute pain. Across a wide range of procedures and surgical interventions, non-opioid analgesics such as liposomal bupivacaine are treating patients without them suffering unnecessary pain or occasioning the risks of misuse and dependency.

5. There are existing structural and regulatory impediments to the widespread adoption of medical practices that forgo the exclusive reliance on opioids. These impediments present themselves across a range of issues, from physician training to federal billing codes and even insurance expectations, such as found with the "bundling" of payments to hospitals and providers. This report examines ways of overcoming these impediments and calls on all parties addressing the opioid crisis to adopt a new calculus of costs and benefits to the patient and to society when considering pain treatment alternatives.

   The report concludes by calling for a new model of patient care, built around a targeted flexibility in the management of pain, incorporating patient involvement and in accord with a better understanding of specific patient vulnerabilities and risks, as a multi-modal framework for treatment is adapted to the particular challenges of each case.

   Such a "preventive medicine" approach to patient care should guide such factors as the future of the drug approval process, of medical training, of patient education, and lastly, the development and adoption of an expanded set of medical practice tools.

Introduction: The Current Scope of the Crisis

> *In some ways, dissolving the bond between potent analgesia and addiction is the holy grail of pain research. One could argue that if a drug were found that was potent across a broad range of painful conditions, was not addicting and to which patients did not develop tolerance, pain would cease to be a significant medical problem. Meanwhile, the debate continues over when and how to use opiate analgesics.*
>
> —Dr. Howard L. Fields, author of "The Doctor's Dilemma"[1]

Recently the Centers for Disease Control and Prevention (CDC) announced that in 2016, the most recent year with complete data, overdose deaths reached a record high of 63,600 deaths in the U.S., two-thirds of which were opioid overdoses.[2] The number appears to have increased even further during 2017, based on preliminary data.

Also in 2016, according to a national survey, about 2.1 million Americans aged 12 or older met criteria for an opioid use disorder (i.e., addiction)—with 1.8 million people with a prescription pain reliever use disorder and 0.6 million with a heroin use disorder.[3]

In just one year, from 2015 to 2016, overdose deaths increased 21 percent. They now exceed deaths from car crashes, guns, and HIV.[4] Drug overdose deaths from all drugs are now the most common cause of death for Americans under the age of 50.[5]

Besides the toll from the use of illicit drugs, legitimate medical practice is also implicated in this epidemic of use and deaths. Opioid prescribing to patients with chronic pain increased the number of Americans taking prescription opioids (97.5 million in 2015), while the sheer prescribing volume increased, for patients and non-patients alike, access to and availability of prescribed opioids.[6] For example, in 2012, 259 million prescriptions for opioids were dispensed in the U.S.–enough for one bottle of opioids for each American adult.[7] [8]

Clearly, some proportion of those exposed through medical practice will suffer from the onset of abuse and dependency. However, as psychiatrist and drug policy expert Dr. Robert DuPont of the Institute for Behavior and Health has written, we have yet to understand fully how non-addicted opioid pain patients transition into opioid addiction, as well as how the medical use of opioids differs from the addictive use of opioid medicines.[9]

Opioid initiation can begin under a doctor's care. For a great number of Americans, their first exposure to opioids comes from legitimate medical practice. It might be through the treatment of chronic pain, especially joint or skeletal pain that may have a long-term dimension, or it might result from an acute medical intervention.

For many, exposure comes through an experience of surgery, where the entire perioperative setting may present various opioids, both in anesthesia and in response to post-surgical pain.

It is now recognized that prescribing for post-surgical pain presents the risk of a long-term, persistent use pattern for the patient, sometimes as a function of the type of surgery and possible complications thereof.

Various studies have provided estimates regarding the number of patients undergoing both major and minor surgery who become susceptible to persistent opioid use. Though the exact percentage varies as a function of the type of surgery, examination of patients at subsequent time periods post-surgery demonstrates that a surprisingly high number who are prescribed opioids for pain are still filling additional prescriptions many months after the surgical procedure.

Further, whether the patient was "opioid naïve" at surgery or had already been exposed to opioids on earlier occasions proves a major variable affecting the percentage of those who will progress to persistent use over time.

For instance, for shoulder arthroplasty, a recent study showed that 9.1 percent of opioid-naïve patients were using opioids six weeks after the surgery, while for opioid-experienced patients, that number jumped to 71 percent.

As found in another study, 6.3 percent of opioid-naïve patients who underwent spine surgery were still on opioids a year beyond the surgery, while for the opioid-experienced, that figure soared to 45.3 percent of patients exposed through surgery. Comparable results have been found in studies regarding other procedures such as bariatric surgery or total knee replacement.

Such figures are troubling no matter how appropriate or well-supervised the initial opioid prescribing; it is indisputable that post-surgical opioid exposure plays some role in conditioning patients to seek persistent use. Moreover, some patients may experience numerous surgeries throughout their lifetimes, with the risk compounding from each opioid exposure.

And finally, one must consider those patients facing the disabling pain of conditions such as end-of-life or cancer pain, for whom long-term opioid prescribing is a significant and appropriate part of care.

Clearly, not all such patients, exposed for whatever reason, go beyond responsible, medically-supervised protocols for their use of opioids. But as shown previously, a percentage of all such patients succumb to various risk factors that may endanger them. Potentially, every opioid exposure presents some risk of a patient becoming conditioned to the effects of the powerful narcotics.

For all patients, one could argue, an appropriate goal for medical practice, particularly in response to acute or chronic pain, would be to reduce where possible occasions of opioid exposure beyond necessity.

Yet while all patients are somewhat at risk, for various subsets of patients—such as those with co-morbidities or genetic predispositions—the risk factors are increased. Perhaps the greatest risk is for that subset of patients who have already experienced substance abuse or dependence, or who have histories of poly-drug use, with other substances taken in conjunction with opioids.

Beyond the role of opioids in abuse and dependency, the relationship between opioids and surging overdose deaths must be understood. While an overdose can occur with any user, the greatest risk has been linked to an additional exposure factor, which is the wider pattern of nonmedical, or recreational, drug use. Opioid overdose deaths most commonly involve a profile of poly-drug use, combining the opioids with substances such as alcohol, marijuana, cocaine, methamphetamine, and others.[10]

This pattern holds even for patients treated for opioid addiction whose first opioid exposure came through legitimate medical practice. Studies have provided evidence that nearly 95 percent of patients reported prior (or coincident) use of other psychoactive drugs, including high rates of alcohol and marijuana use among their other drug use.[11]

The number of substances involved can be striking. One study in Florida reporting toxicological outcomes of overdose cases found that 95 percent of opioid deaths involved other drugs, sometimes multiple drug exposures (from 2 to 11 total substances) in addition to the opioids.[12]

Additionally, there is now a better understanding of how adolescent initiation to drug use of any type contributes to opioid overdose susceptibility at older ages.[13] Early developmental exposure to marijuana, for instance, substantially elevates the risk of subsequent dependence on other substances of abuse, including opioids.

This risk is particularly great when youth consume high-potency marijuana daily. If a person has not initiated drug use before early adulthood, they are at far less risk of ever developing a substance use disorder, indicating that successful youth prevention measures that at least delay substance initiation will pay long-term dividends in reduced dependency and damage.

Although first use of an opioid, for many, came from a physician's prescription, the majority of even these individuals initiated drug use with some other substance before encountering opioids.[14]

Much has been made of the role of the increase in prescription opioid availability and the rise of the opioid addiction and overdose crisis, including the contribution to that crisis of illicit opioids from criminal transactions. Some critics even blame the attempt to limit the supply and access to prescription drugs of abuse as having created a perverse incentive to seek out illicit opioids instead.

The transition, or "cross-over," from prescription opioid use to illicit use of drugs such as heroin is a real threat, but recent data have shown it is not common. Of those who misuse opioids non-medically, about 4 percent will initiate heroin within five years of first prescription opioid use.[15] Once again, it seems that patients who were already poly-drug users prior to their medical prescription will be those most at risk of adding illicit opioids to their drug dependency.

The point is that while any patient who is prescribed opioids can experience, depending on dosage and duration, symptoms of tolerance and withdrawal from the medications, the patients most at risk of exceeding dosage expectations established by the physician are very commonly those with a prior history of substance misuse.

Unless patients take medications in ways and at dosages not prescribed, they are at smaller risk of addiction, or of using opioids along with other drugs of abuse.[16] Hence, when deciding whether to prescribe opioids, it is important to disaggregate patients by evaluating whether they face enhanced risk from further exposure. For such patients, non-opioid alternatives for pain should offer important choices.

Also, according to responses to the *National Household Survey on Drug Use and Health*, at least 50 percent of people who misuse opioids access them from friends and family, implying that unused/unneeded opioids, rather than direct contact with a prescribing physician, are supplying a significant population of users.[17]

In this sense, the impact of the strict doctor-patient relationship involving opioid prescribing is not limited to that patient, but may instead "spill over" into the wider public health challenge.

Why Alternatives to Opioids Represent a New Medical Responsibility

There are multiple routes by which Americans have become trapped in inappropriate opioid exposure or opioid dependency, leading to the worst drug crisis in our nation's history, measured in terms of human life lost and in terms of social and economic costs.

For each of the pathways that has led to opioid exposure and the risk of dependency, particularly those involving chronic pain, there are now urgent policy responses seeking to ameliorate the crisis.[18]

One devastating pathway into adverse consequences has been through the portal of generalized substance abuse involving the illicit drug markets. Importantly, as has been noted, an overwhelming number of current opioid users and potential overdose victims have histories of poly-drug abuse, to which the potentially lethal opioids are added.[19] That is, some people clearly arrive at an opioid crisis of abuse or dependency from a pathway independent of exposure under medical supervision.

Moreover, as noted in the previous section, studies of overdose victims reveal the true extent of poly-drug exposure contributing to opioid lethality. Most victims are found with multiple drugs in their system, each of which can impair judgment as well as exacerbate the lethal risk of the opioid exposure.[20]

While opioid prescribing has been a significant force behind the current epidemic of use and its consequences, it is important to acknowledge the corresponding steep increase in the supply of illicit opioids, such as surging heroin production from Mexico and now synthetic opioids from rogue labs in both Mexico and China.

That is, the overall trajectory of the opioid crisis has shown a major shift from being driven by pharmaceutical diversion and misuse to a profile of illicit opioids playing the dominant role. Prescription deaths have, as of 2016, declined somewhat, while heroin and (illicit) fentanyl-related deaths have risen steeply.

The latest data available, found in a report in the *Journal of the American Medical Association* in May 2018, show that among 42,249 opioid-related overdose deaths for 2016, 19,413 involved synthetic opioids, 17,087 involved prescription opioids, and 15,469 involved heroin.[21]

Synthetic opioid involvement in these deaths increased significantly from 3,007 (14.3 percent of opioid-related deaths) in 2010 to 19,413 (45.9 percent) in 2016. Among synthetic-opioid related deaths in 2016, 79.7 percent involved another drug or alcohol.[22]

Clearly, these two dimensions of the opioid crisis have reinforced each other. Our policy responses must counteract both dimensions by simultaneously shutting down the supply of illicit (and especially lethal) opioid substances while also transforming medical practice in the direction of non-opioid alternatives for managing pain.

It is also important to acknowledge the extent to which suicide is affecting overdose rates. The realization that some opioid overdoses appear to derive from desperation, and are intentional rather than inadvertent, holds important lessons.[23]

First, suicide may be a somewhat neglected toll of opioid misuse, in that it leads some people into a sense of hopelessness, escape from which can only come from self-harm.

Second, the availability and ready presence of opioid medications, or illicit drugs themselves, may be factors in sharpening the lethality of a suicide attempt. In either case, this pathway is a tragic additional dimension of our current crisis.

What should our public health policy response be? Given the multiple dimensions in play, we should be crafting responses to the critical illicit drug dimension of the crisis, relying on public health, criminal justice, and national security strategies to intervene and interrupt the surging supply and availability of these substances, largely from international sources, and to move those suffering into treatment and recovery.

But it is imperative to focus attention on medical practice itself as a critical pathway to opioid exposure and its potential risks of abuse, dependency, and death. This pathway opens as patients are exposed, through mainstream and legitimate medical practice, to opioid use in response to a host of maladies, most often involving either acute or chronic pain.

Even in the absence of the onset of abuse or dependency, there is today a greater recognition of adverse outcomes involving long-term prescribing of opioids, even to patients who are fully compliant with appropriate protocols.

There are multiple morbidities associated with extended opioid use (including such developments as hyperalgesia, or increased sensitivity to pain). For instance, as was noted in 2012,

> Opioids cause adverse events in several organ systems.... Opioid-related adverse effects can cause significant declines in health-related quality of life and increased health care costs ... [leading to] recommendations for judicious and selective opioid prescribing for chronic non-cancer pain by primary care physicians.[24]

In other words, it is important to realize that the potential harm from long-term opioid prescribing carries risks for the patient even when careful medical supervision prevails. This is true for many medical interventions regarding pain, but narcotics also carry additional risks, which are the dangers of developing abuse and dependency.

Opioid prescribing, especially at high doses and for long periods, can become a pathway for some patients (often those with additional co-morbidities) that escalates quickly, moving from approved prescriptive use into inappropriate and unsanctioned drug use, outside the scope of proper medical supervision.

Moreover, so troubling is this unintended outcome that physicians report that patients with histories of opioid misuse who are in need of medical procedures will forestall or

express reluctance to undergo the procedures because of their concerns that additional opioid exposure places them at risk. Physicians themselves are addressing ways to provide interventions for those with known histories of risk for abuse.[25] [26]

Though we have identified two distinct pathways for vulnerability to opioids, in reality they interact. The iatrogenic pathway from medical practice also affects the illicit dimension, as it is sustained not only by unscrupulous or fraudulent prescribing, but by diversion of the opioids outside of medical supervision.

Given the greatly expanded reliance on opioid prescribing over the past decade, the sheer number of opioid dosage units in circulation has greatly amplified the risk of improper diversion and use.[27]

This medical dimension of the crisis, even though the initial source is sanctioned and regulated, also requires policy interventions on par with the illicit supply problem. Accordingly, multiple guidelines, policy changes, and shifts in medical practice are currently underway, seeking to re-shape or even transform how medicine has come to rely on opioids in response to acute or chronic pain.

It is important to explore one common scenario that all too often leads to devastating complications. A patient suffering from an orthopedic condition requires surgery. In addition to the anesthesia necessary for the surgical procedure itself, the patient, throughout the perioperative period, will often be provided with opioid medications, varying in dose and amount by the type of procedure, the characteristics of the patient, the success of the surgery, and various other factors.

For some proportion of patients—in particular, those with a history of substance use or some known psychological risks—they have now entered a period of enhanced risk. Through their exposure to opioids, some patients become conditioned to persistent use and also experience a growing reliance on the drugs, both physical and psychological.

Not uncommonly, physicians have continued to provide the medications even in the face of indications that patients were getting into trouble, and even following such dire developments as a non-fatal overdose. Often, they are pursuing their sense of best medical practice and responding to patient expectations.[28]

Too frequently, for a variety of reasons, the patient may be given what in hindsight seems like an excessive number of dosages for an extended period of time. The patient's risk grows with high dosage and longer periods of use, as well as with interactions with additional drugs prescribed.[29] [30]

Yet for other patients, a surprisingly large number of dosages prescribed—as many as two-thirds—may be unused after each surgical episode, according to a paper on surgical outcomes from the Mayo Clinic reported at the most recent meeting of American Surgical Association.[31]

Important Lessons

This last finding regarding the scope of unused medications clearly indicates not only that doctors are currently overprescribing opioids as a default, but that many patients appear to be already exercising their own discretion regarding the need for, and the risks of, extended opioid use. This fact may bolster attempts to provide non-opioid alternatives to patients.

Nonetheless, standard medical practice has now inculcated two parallel risks related to opioids, however inadvertently. Not only will some percentage of patients begin to seek opioids in a persistent (or even abusive) profile, but the large volume of unused medications becomes a source for diversion, whereby medications prescribed are either shared inappropriately or even sold in illicit transactions.

Thus, the two major routes of the opioid crisis—the medical practice and the illicit drug market—have in fact reinforced each other.

Is Cutting Access to Opioid Medications a Sufficient Response?

In response to the growing crisis of unintended outcomes from widespread opioid prescribing, efforts to circumscribe the sheer volume of prescriptions have begun to take effect.

While this is welcome news, opioid prescription totals in the United States, while decreasing from 2011 to 2015, were still three times higher in 2015 than they were in 1999, according to the CDC.[32] And from 1999 to 2016, the number of opioid overdose deaths increased fivefold, including a period of time when nationwide prescribing was actually in decline, according to another CDC report.[33]

Now that this pathway of risks for patients and the enormous public health toll driven by well-intended medical practice are more apparent, one immediate policy response, as found in the 2016 "CDC Guideline for Prescribing Opioids for Chronic Pain," has been to call for even more dramatic reductions in the prescribing, use, and overall availability of opioid medications.[34]

The issue of curtailing prescribing has received high-level political attention. President Trump recently called for a reduction in opioid prescribing of over one-third within three years, notwithstanding some policy resistance to abrupt medication reductions without better targeting of patient risks.[35] [36]

Further, the Drug Enforcement Administration (DEA), under congressional pressure, has recently proposed sharp limits on their opioid quota-setting system, thereby limiting the production potential of pharmaceutical manufacturers. This effort has also met with resistance from some quarters.[37]

The "CDC Guideline" has been followed by numerous similar calls, including pending congressional action, for even more drastic reductions in opioid prescribing.

For instance, bills currently before Congress are moving toward the imposition of even greater limits, employing multiple federal agencies. As *Roll Call* notes,

> The [draft Senate] bill would affect the NIH, the FDA, the CDC, the Drug Enforcement Administration, the Substance Abuse and Mental Health Services Administration, and the Health Resources and Services Administration, as well as provide support for families and workers affected by the opioid crisis.[38]

Multiple efforts to drive down opioid use are underway, and have generated resistance from some patient groups and some physicians, in some measure because of their one-dimensional metric for success.[39] For example, this year the Centers for Medicare and Medicaid Services proposed a rule that would restrict opioid doses to Medicare patients to only 90 morphine milligram equivalents (MMEs) per day.[40] An estimated 1.6 million Medicare beneficiaries reached that threshold at least one day in 2016.

For critics, such prescribing thresholds potentially lead to decreased quality of life, as they provide "no metric for success other than reducing certain measures of prescribing.... Neither patient access to care nor patient health outcomes are mentioned." [41]

As Dr. Stefan Kertesz and Dr. Sally Satel have further argued,

> If the agency goes through with this element of the plan, it will basically be joining half of all states that restrict duration of opioid analgesia to somewhere from three to 10 days, depending upon the state. Some pharmacy benefit managers, the pharmaceutical industry, some insurers, and the American Dental Association have enacted or demanded prescribing limits as well.[42]

Moving beyond a simple call for prescribing reductions, one Senate bill calls for more flexibility by the National Institutes of Health in researching non-addictive painkillers that could be alternatives to opioids.[43]

Yet this Senate bill goes beyond even the "CDC Guideline" in limiting opioid prescriptions to three days. Unintended consequences threaten to follow, including reports of non-consensual opioid dose reductions for patients.

This pressure to reduce opioid MMEs comes notwithstanding the positive news that various policy and medical practice interventions have already led to substantial reductions, since their height in 2012, of both MME doses and the overall number of opioid prescriptions.

In fact, the decline in opioid prescribing is substantial and can be seen nationwide affecting not only the number of prescriptions written, but also the overall total of MMEs. The CDC in a 2017 report indicated a decline from an all-time peak of 783 MMEs per capita in 2010 to 640 MMEs per capita in 2015, an 18 percent drop, accompanied by the

corresponding decrease in the sheer quantity of opioid prescriptions and number of pills in circulation.[44]

Some policy critics and many in the media have raised one further risk of such reductions, which would be the incentive for chronic pain patients faced with reduced access to opioids to resort to illicit, and vastly more deadly, black-market alternatives. The risk appears to be real, albeit perhaps overstated and not of the scope found in many popular accounts.

For instance, the development of an abuse-resistant formulary for OxyContin led to, perversely, increased risk from heroin.[45] Though opioid pills have been cited as a common pathway for subsequent heroin initiation, recent data have shown a steep rise in the percentage of heroin users who initiated with heroin itself.[46] As one study concluded,

> In 2005, only 8.7% of opioid initiators started with heroin, but this sharply increased to 33.3% ($p<0.001$) in 2015, with no evidence of stabilization. The use of commonly prescribed opioids, oxycodone and hydrocodone, dropped from 42.4% and 42.3% of opioid initiators, respectively, to 24.1% and 27.8% in 2015, such that heroin as an initiating opioid was now more frequently endorsed than prescription opioid analgesics.[47]

In other words, some who initiate their exposure through illicit markets are likely to seek out pharmaceutical sources to supplement or supplant their high risks of lethal exposure from illicit supplies. This illustrates yet another potential interaction between the medical and the criminally illicit pathways to the opioid crisis.

Looking at another side of the ledger, as over-prescribing is sharply reduced, there is the real prospect of legitimate patients being unconscionably left with untreated pain if opioids are withheld.[48]

To grasp the scope of the problem, the 2012 National Health Interview Survey found that an estimated 25.3 million U.S. adults (about 11.2 percent) reported pain every day for the previous three months and nearly 40 million adults (17.6 percent) had severe pain.[49]

As noted, there are already pressures from both physician and patient groups to resist new opioid policy guidelines as being too drastic and potentially harmful for some patients. As the *Wall Street Journal* reported on April 26, 2018, "Patient groups and health care providers are increasingly challenging the limits placed on prescription opioids in the name of combating the epidemic."

Hence, the medical practitioner stands between the horns of a dilemma, placing patients at some risk by either continuing, or by sharply discontinuing, opioid prescribing.

Developing Models of Pain Management: A New Scenario

There is a dual policy imperative: reduce excessive opioid prescribing, while ensuring appropriate utilization and access to alternatives to alleviate untreated pain. It is in this context that providers are now developing a flexible and multi-modal approach to pain, such as the experience of surgical pain, that utilizes, in a staged fashion, opioids where necessary, supplemented by an array of analgesic tools and medications to improve patient outcomes.

It is now possible to envision a new scenario for patient care utilizing all of the tools available under a multi-modal response to pain. A patient prepares for a major orthopedic surgery having been fully informed of their options, thereby enabling some degree of patient choice in their own pathway.

A trained physician or practitioner team, having assessed the particular risks and prognosis for particular surgical interventions, evaluates the patient's optimum profile for a successful outcome, including the patient's co-morbidities and substance-use history. The patient becomes part of a well-educated team with well-described expectations for responding to perioperative pain.

Under a multi-modal approach, beginning with a standard anesthesia protocol using a synthetic opioid such as fentanyl, the patient undergoes the orthopedic procedure accompanied by, as a possible option, a surgical infiltration involving an immediate as well as a long-acting analgesic local or regional injection that provides a non-opioid drug that suppresses pain in affected nerves.

Post-surgery, the patient continues to experience the local or regional analgesia, and is provided, depending on the physician's judgment and the patient's expectations, additional non-opioid analgesia to manage outcomes.

The ideal result is not only that the exposure to opioids is reduced substantially and the overall circulation of unused opioids curtailed, thereby mitigating both patient and societal opioid risks and costs, but equally important, patient outcomes are improved.[50] Compared to the excessive costs of opioid reliance, such superior outcomes should result in improved patient flow and discharge, as well as for criteria such as recovery and ambulatory improvements, fewer readmissions to the hospital, and reduced hospital costs.

The long-term result will likely provide superior patient well-being and more effective medical practice. Additionally, the goals of reducing the opioid crisis will be provided for without the consequence of untreated pain.

Empirical Support for Non-Opioid Alternatives

Evidence is strong that a variety of analgesic alternatives already exist (or are in development) that could not only benefit patient outcomes, but further reduce hospital costs, lower rates of readmission, and reduce the adverse societal impact of excessive opioid reliance.

According to Stanford Neurosciences Institute pain specialist Dr. Sean Mackey, there are more than 200 analgesic compounds known that could be better incorporated into pain treatment, or could serve as a basis for new developments.[51] Yet while new developments are encouraging, we have effective alternatives at hand already.

As Dr. Mackey's Stanford colleague, Dr. Keith Humphreys, wrote in the *Washington Post*, "The problem in American medicine is not a lack of alternatives to opioids, but the minimal utilization of the many non-opioid treatments for pain that already exist."[52]

Such alternatives include recognition of standard analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), which can be used in conjunction with opioids or even as replacements, along with research options only now in development. Evidence is accumulating that several alternatives are serving patient needs and reducing opioid risks.[53]

One example showing promise involves brain peptido-mimetics, offering drugs that could act on pain receptors but not activate dependence or tolerance dimensions. They are being studied in animal models at the University of Michigan.[54]

A recent study in the *Journal of the American Medical Association* found that for chronic back pain, or hip or knee osteoarthritis pain-related function measured at 12 months, treatment with opioids was not superior to treatment with non-opioid medications.[55]

Similarly, a study of gynecologic surgery outcomes reported declines of almost 90 percent in opioids prescribed after implementation of a restrictive protocol, including a 73-percent reduction in the number of pills dispensed after open surgery, with non-opioid alternatives being sufficient to manage patient outcomes.

Likewise, an examination of dental procedures found that non-opioids such as NSAIDs, at both over-the-counter and prescribed doses, were sufficient analgesics for most post-operative pain.[56]

For total knee arthroplasty, another study demonstrated that a multi-modal response, including an adductor canal nerve block at surgery, controlled pain and reduced opioid reliance, concluding,

> Tailored clinical pathways designed to facilitate early ambulation can reduce hospital length of stay, reduce opioid consumption, reduce antiemetic use, and improve pain control. The results establish that refined clinical pathways can assist in improving care while increasing value to patients, providers, and systems.[57]

In addition, several recent examinations of multi-modal recovery pathways that use the non-opioid medication liposomal bupivacaine have consistently reduced opioid consumption by patients undergoing such diverse surgeries as breast reconstruction, colorectal procedures, shoulder arthroplasty, hysterectomy, and laparotomy involving gynecologic malignancies, while at the same time being associated with enhanced recovery, fewer complications, and reduced hospital stay.

These developing surgical procedures, such as reliance on analgesic liposomal bupivacaine with an extended-release infiltration at the time of surgery, have already met with Food and Drug Administration (FDA) approval.[58]

Among these encouraging results, the Mayo Clinic has done work to refine opioid prescribing practices post-surgery. Mayo Clinic internal guidelines were developed to guide orthopedic surgery, a collaborative effort involving physicians, pharmacists, pain medicine specialists, and research scientists, examining opioid prescribing for 25 common surgeries.[59] Research studies based on the Mayo guidelines have been positive.

For example:

> The study compared opioid prescriptions and refill rates for knee and hip replacement surgery patients on the Rochester campus of Mayo Clinic who hadn't received a prescription in the previous 90 days. The team compared 751 patients during the five months after the guidelines took effect (August-December 2017), to the 1,822 hip and knee patients during 2016 who met those criteria.
>
> The authors found that the median prescription dropped 48 percent, from the equivalent of roughly 95 pills of five-milligram oxycodone to about 50 pills. Overall, the middle 50 percent range of prescriptions decreased from about 70-115 pills to 45-50 pills. They also report no statistically significant change in refill rates.[60]

Important lessons from the Mayo effort include the realization that guidelines for prescribing of a general nature, such as those issued from the CDC, need to be supplemented with "procedure-specific" guidelines to provide appropriate outcomes for patients, and, further, that it is important to "counsel patients before surgery on pain expectations."

The Wider Policy Context of Transforming Medical Practice

Given the complexity of medical practice and standards of care, it should be no surprise that there are still impediments to the full adoption of such non-opioid analgesics referenced above, and even for the multi-modal deployment of several alternatives as opioid adjuncts. Today's policy task is to identify and reformulate the factors proving to be barriers to pain treatment goals.

The task is complex, as the barriers include patient education regarding their options as consumers, physician education, and even training in medical procedures to learn the most effective and beneficial choices. Additional barriers must be addressed in regulatory policy, insurance reimbursement rules and codes, the drug and procedure approval process, and even in legislative efforts to guide medical treatment.

It is particularly important to address the various financial incentives found in current insurance reimbursement rate policies; if not adjusted for the adoption of non-opioid alternatives, they can prove to be impediments to public health goals.

An example of a specific regulatory hurdle can be found in Medicare's custom of "bundling" hospital and surgical procedures. Bundling is an effort to fold into one submission for insurance reimbursement a compound set of activities involved in one episode of care.

Although insurance companies would like to encounter more line-item "un-bundled" claims, the use of opioids, and hence their costs in anesthesia and during the perioperative period, very often gets incorporated in a bundled submission.

This practice can become a barrier to new entrants into analgesia, as their drug or surgical practice may be judged to be an additional cost for procedures. For some alternatives involving a new procedure, existing *International Classification of Disease, Tenth Revision* (ICD-10) codes may not provide effective billable codes for the practices.

For example, an infiltrated, extended-release nerve block to address surgical pain not only requires some training for the surgeon and anesthesiologist, but may also be added to the insurance claim over and above the "bundled" cost of opioid prescribing.

It was recognition of this hurdle that led President Trump's White House Commission to Combat the Opioid Crisis to recommend addressing the need for appropriate bundling reforms in order to encourage alternatives. Specifically, the Christie Commission listed as its Recommendation No. 19 that the Center for Medicaid and Medicare Services,

> review and modify rate-setting policies that discourage the use of non-opioid treatments for pain, such as certain bundled payments that make alternative treatment options cost prohibitive for hospitals and doctors, particularly those options for treatment immediate post-surgical pain.

While it is important to acknowledge the recent and welcome emphasis on promoting research "partnerships" between private industry and entities such as the National Institutes of Health to provide emergent non-opioid alternatives, that development alone may not be sufficient if we do not have a comprehensive campaign to incentivize the resultant products.[61] As Stanford's Dr. Humphreys has concluded,

> If Congress simply supports the development of a new non-opioid pain treatment that, like all the others, rarely gets prescribed, it will do little to ameliorate the simultaneous problems of poorly managed pain and opioid overprescribing. It could have a much bigger effect by enhancing insurance benefits (e.g., in Medicaid and Medicare) for psychological and behavioral pain care services provided by interdisciplinary pain management clinics as well as funding training for pain management in medical schools and continuing education programs serving physicians and other health-care professionals.[62]

Moving Toward a Preventive Medicine Approach to Patient Care

Given the rapidly changing profile of the opioid crisis and the impact of illicit opioids, medical prescribing today may not be the largest driver of the overdose and addiction crisis. That said, medical practice is still a significant cause of the crisis and it presents the advantage that we can do the most about it from a policy point of view.

It is well within our grasp, from a medical education and regulatory purview, to gain leverage over the epidemic, thereby saving lives while also providing alternative pathways to avoid needless patient suffering.

The medical practice contribution to our current crisis admits of multiple dimensions. There has been an inadvertent complicity on many sides, ranging from physician practice to pharmaceutical pressures to broaden opioid use, from DEA quota-setting to diversion control, and from contradictory regulatory control to the role of medical advertising. Add to that medical reimbursement rules, problems with the FDA approval process, as well as patient demand, pharmaceutical negligence and avidity, and legislative pressure from Congress. Even peer-reviewed medical science literature and journalism have played a pernicious, or at best a diffident, role in contributing to our dilemmas, as author Sam Quinone notes in "Dreamland: The True Tale of America's Opiate Epidemic."

Wherever a contributing party is identified, a comprehensive intervention must include an understanding of where we were deficient *and* a strategy for leveraging that dimension with policy changes.

Opioid medications are embedded in these multiple structures, as they are in complex patient-doctor interactions and pressures. Problems include the complexity of pain, of symptoms both physical and psychological, of complications involving everything from genetic predisposition to depression to poly-drug substance abuse. Finally, there is the propensity to follow, unwisely, the path of least resistance in alleviating pain by providing yet more opioids to patients already at risk.

Of course, there is a subset of patients for whom opioids are properly reserved *in extremis*. In cases of chronic or end-of-life deterioration and suffering, the balance of risk and benefit begins to shift back toward full opioid utilization. That is, the response should not inadvertently contribute to a loss of the proper place of opioid prescribing.

But targeted flexibility in the management of pain, guided by a disaggregation of patient histories and requirements, is obtainable. A better framework would rely on a new comprehension of the costs, to society and to patients, of unfettered opioid promotion, and of an evaluation of the benefits of opioids to patients and to public health.

It seems desirable that our evaluative understanding of alternatives to opioids should be submitted to a new cost-benefit calculus that takes systematic account of opioid complications, as well as what economists refer to as the "externalities" of opioid

overprescribing. Such a new calculus should guide the future of the drug approval process, of medical training, and the development and adoption of an expanded set of medical practice tools.

About the Authors

David W. Murray

David W. Murray is a Senior Fellow at Hudson Institute where he co-directs the Center for Substance Abuse Policy Research. While serving previous posts as Chief Scientist and Associate Deputy Director (Supply Reduction) in the federal government's Office of National Drug Control Policy, Murray directed extensive scientific research on all aspects of the drug problem and helped coordinate high-level interagency efforts to limit the production of illicit drugs and counter the transnational criminal organizations that control their global shipment and marketing.

He is the author of numerous scholarly papers, essays, and commentaries; co-author (with Joel Schwartz and S. Robert Lichter) of the widely noted book "It Ain't Necessarily So: How Media Make and Unmake the Scientific Picture of Reality"; and a frequent guest on major network television and radio programs.

John P. Walters

John P. Walters is Chief Operating Officer of Hudson Institute and Director of Hudson Institute Political Studies. As COO, Mr. Walters oversees the Hudson Institute's operations, including staff and research management. From December 2001 to January 2009, he was director of the White House Office of National Drug Control Policy and a cabinet member during the Bush Administration.

As the nation's "drug czar," Mr. Walters guided all aspects of federal drug policy and programs—supporting efforts that drove down teen drug use 25 percent, increased substance abuse treatment and screening in the healthcare system, and dramatically dropped the availability of cocaine and methamphetamine in the U.S. He also helped build critical programs to counter narcoterrorism in Colombia, Mexico, and Afghanistan.

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Hudson Institute
1201 Pennsylvania Avenue, N.W.
Suite 400
Washington, D.C. 20004

P: 202.974.2400
info@hudson.org
www.hudson.org