

## EDUCATIONAL OBJECTIVES

At the end of this continuing education activity, pharmacists and pharmacy technicians will be able to

- Review the factors involved in drug overdose lethality
- Describe the impact of prescription opioids on the problem of drug overdose
- Characterize regulatory approaches aimed at reducing opioid prescribing
- Discuss how the efforts to reduce diversion have affected patients being treated for pain



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ACPE UAN: 0009-0000-21-061-H03-P  
0009-0000-21-061-H03-T

Grant funding: NONE

Cost: Pharmacists \$7  
Technicians \$4

INITIAL RELEASE DATE: October 19, 2021

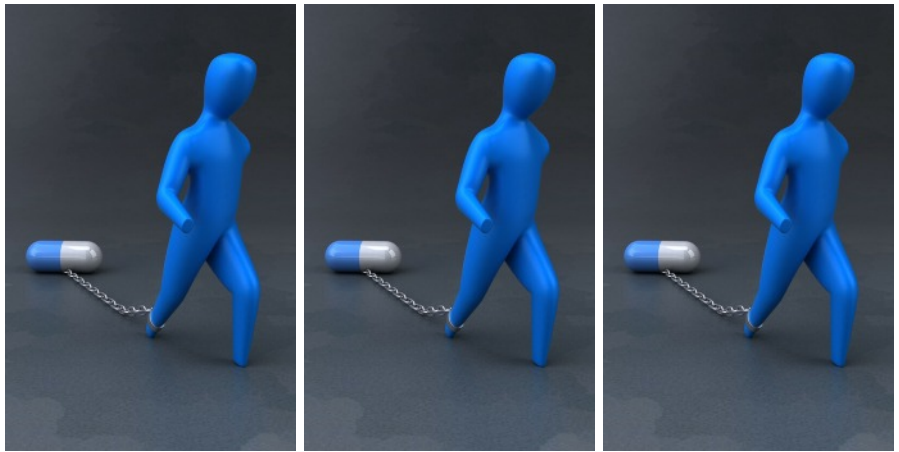
EXPIRATION DATE: October 19, 2024

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## LAW: CONFRONTING THE PRESCRIPTION OPIOID CRISIS: THE PENDULUM SWINGS

**ABSTRACT:** Drug overdose deaths have been rising for three decades and reached a new record in 2020, fueled principally by opioids. Lethality due to prescription opioid drugs dominated the early part of the epidemic and still account for a significant number of deaths. This period was characterized by a desire to treat pain adequately and resulted in rampant prescribing. Later, clinical guidelines and regulatory efforts sought to reduce the use of opioids and successfully discouraged opioid use. This continuing education activity traces the role of prescription drugs in the development of the opioid epidemic and the regulatory response. It also examines health care professionals' responsibility to reduce diversion and how the application of the regulatory changes have adversely affected patients being treated for pain.

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**FACULTY DISCLOSURE:** The authors have no actual or potential financial conflicts of interest associated with this article.

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## INTRODUCTION

*"We have two public health crises going on at the same time: one is undertreated pain and the other is prescription drug abuse. As we treat one of those problems and get doctors to treat more aggressively for pain, we're simultaneously seeing numbers go up related to prescription drug abuse—and no one knows with any certainty if one is driving the other."<sup>1</sup>*

Scott M. Fishman, MD, chief of the Division of Pain Medicine at the University of California, Davis.

Although Americans drove less in 2020 due to the pandemic, projections from the National Highway Traffic Safety Administration (NHTSA) show that an estimated 38,680 people died in motor vehicle traffic crashes; this is the largest yearly total of fatalities since 2007.<sup>2</sup> Yet, while these numbers are staggering, pharmacy staff likely already know that the estimated 93,331 drug overdose deaths in 2020 overshadows the traffic accident figure.<sup>3</sup>

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Pharmacy personnel are aware of the drug overdose crisis in the U.S. The number of overdose deaths for the year ending December 2020 is the highest total ever recorded and far eclipses the 71,130 deaths reported in 2019.<sup>3</sup> The 2020 result is also the largest annual increase in at least three decades.<sup>4</sup> More than 70,000 of these deaths (over 70% of the total) were associated with overdose of opioids.<sup>3</sup> The troubling numbers have been largely attributed to the continuing surge in the use of the more deadly opioid, fentanyl, and the 2020 COVID pandemic's destabilizing effects.<sup>4,5</sup>

The number of opioid deaths has been increasing for several decades.<sup>5</sup> Much of the blame for the opioid crisis's initial escalation has been placed on the misuse of prescription opioids. Health care professionals, including pharmacists, have been criticized for contributing to the crisis through the massive prescribing and dispensing of opioid analgesics.<sup>6</sup> Pharmacy personnel have a responsibility to prevent misuse of controlled substances. Over the past decade, regulatory and public health efforts have focused on changing prescribing and dispensing habits in an effort to reduce the supply and diversion of opioids and other controlled substances.

This continuing education activity will review the evolution of the opioid crisis and some regulatory and public health strategies aimed at diminishing the impact of prescription opioid overdose. It will also address the predicament faced by pharmacists and other health care professionals in implementing these approaches.

## THE PREDICAMENT

A new patient presents a prescription to your pharmacy for a large quantity of opioids. The prescriber—unknown to you—has a practice about 100 miles away. The patient says he does not have insurance and will pay cash. His appearance is not unusual, but he is showing signs of agitation and anxiety and claims to be in severe pain. What will you do? Will your decision expose you to risks?

## THE OPIOID CRISIS

Drug overdose fatalities have risen dramatically for three decades (except for a small decline in 2018).<sup>5</sup> Yearly fatalities have quadrupled since 1999 and reached the new record of 93,331 in 2020.<sup>7</sup>

Opioids have been the main driver fueling the overdose crisis, and today over 70% of overdose fatalities are associated with opioids.<sup>8</sup> The impact of the opioids has occurred in three waves.<sup>7</sup> The first wave starting in the 1990s was due to prescription opioids and was likely the direct result of an increase in opioid prescribing.<sup>7</sup> The second wave began in 2010 and was due to heroin overdoses. The third wave began in 2013 and was fueled by deaths resulting from synthetic opioids especially non-prescribed fentanyl and related analogs.<sup>7</sup> This last wave

continues today with 36,359 deaths due to fentanyl in 2019 [likely surpassing 50,000 when final 2020 data are reported].<sup>5,9</sup>

## Prescription Opioids

***“So, consider the amount of standard daily doses of opioids consumed in Japan. And then double it. And then double it again. And then double it again. And then double it again. And then double it a fifth time. That would make Japan No. 2 in the world, behind the United States.”***

- Drug policy expert Keith Humphreys.<sup>10</sup>

Although heroin and illegally manufactured fentanyl are now the primary contributors to opioid overdose, misuse of prescription drugs has long been a key factor and remains so today. Opioid prescribing accelerated rapidly in the 1990s, apparently without a corresponding increase in reported pain.<sup>11</sup> In the 1990s, various parties assured the medical community that the risk of addiction to prescription opioids was low; prescription rates increased.<sup>12</sup> Between 2007 and 2012, opioid prescriptions per capita rose by 7.3%, while total prescriptions per capita rose only 3.5%.<sup>13</sup>

In all, health care providers wrote 259 million prescriptions for opioid pain medication in 2012, equivalent to one prescription for every adult in the United States.<sup>14</sup> National per capita consumption of oxycodone went from around 10 milligrams in 1995 to almost 250 milligrams by 2012.<sup>15</sup> More than 100 million prescriptions were written for hydrocodone/acetaminophen combination products alone in 2005, far exceeding the 63 million prescriptions for the second most prescribed drug (atorvastatin).

Hydrocodone/acetaminophen combination products continued as the most prescribed drugs for much of the decade.<sup>1</sup> In West Virginia, a state with 1.8 million residents at the epicenter of the opioid crisis, 780 million dose units of oxycodone and hydrocodone were dispensed between 2007 and 2012.<sup>15</sup> In one community with a population of only 2,900, more than 20 million opioid prescriptions were processed over a 10-year period.<sup>15</sup> Not surprisingly, many of these prescriptions were diverted to illicit use, facilitated by unrestrained distribution, rogue pharmacies, Internet sales, unethical physicians, and patients whose legitimate opioid medications were stolen, or who sold them for profit.<sup>16</sup> Drug overdose death rates also sharply increased.<sup>9,16</sup>

## How Did We Get Here?

Many factors drove the prescription opioid overdose epidemic.<sup>12,16,17</sup> These include:

- A well-intentioned effort by the medical community to manage chronic pain better
- Deceptive marketing claims about addiction to new, longer-acting opioids
- Lack of physician and pharmacist education on the use of drugs with high abuse potentials
- Direct-to-physician marketing
- Pill mills

## The Infamous Letter: “Addiction Rare in Patients Treated With Narcotics”

Published in the *New England Journal of Medicine* in 1980, the letter with the above title was written by Hershel Jick and his assistant Jane Porter of the Boston Collaborative Drug Surveillance Program at Boston University Medical Center. It was a short one-paragraph submission with fewer than 100 words. Unfortunately, researchers believe it became a major contributor to today's opioid crisis. Hundreds of articles have cited this letter, with many—if not most—citing it years after its publication and grossly misrepresenting its conclusions.

Jick, who wrote the letter, said in a 2017 interview, "The letter wasn't of value to health and medicine in and of itself. So if I could take it back—if I knew then what I know now, I would never have published it. It wasn't worth it."

– National Public Radio

<https://www.npr.org/sections/health-shots/2017/06/16/533060031/doctor-who-wrote-1980-letter-on-painkillers-regrets-that-it-fed-the-opioid-crisi>

## Pain Management Practice Guidelines

The 1990s ushered in a period of revised thinking about how to manage chronic pain and a belief that pain was being undertreated. This period was typified by intensified lobbying by patient advocacy and professional groups calling for increased use of opioids to treat pain.<sup>17</sup> Health care and regulatory organizations called attention to pain management and palliative care and supported the use of opioid therapy. These efforts led to the implementation of guidelines, policies, and consensus statements endorsing expanded access to powerful analgesics with an accompanying increase in prescribing.<sup>17</sup>

The American Pain Society introduced a campaign entitled “Pain is the Fifth Vital Sign” in 1995 and encouraged more aggressive use of opioids for non-cancer pain.<sup>12,18</sup> In 1997, the American Academy of Pain Medicine and the American Pain Society issued a joint consensus statement stating that clinicians often managed pain inadequately despite the ready availability of safe and effective treatments. They indicated that the potential of legal or regulatory sanctions related to the prescribing of opioids contributed significantly to this mistreatment of pain.<sup>18</sup> The Federation of State Medical Boards undertook an initiative to develop model pain management guidelines.<sup>19</sup> The organization commented that undertreatment of pain is recognized as a serious public health problem that results in a decrease in patients’ functional status and quality of life. They urged state medical boards and other health care regulatory agencies to adopt policies encouraging adequate treatment of pain, including the use of opioids when appropriate.

In 2000, Congress declared 2000–2010 the Decade of Pain Control and Research. Its objective was to recognize a new emphasis on pain management and palliative care, stating “physicians should not hesitate to dispense or distribute controlled substance when medically indicated.”<sup>20</sup> Many international health organizations expressed the view that pain relief was a human right.<sup>21</sup>

These sentiments from professional and governmental institutions spurred a change in the attitude towards opioids so that they were no longer reserved for acute or terminal pain and use

expanded to treat any painful condition.<sup>6</sup> Moreover, accrediting bodies and reimbursement agencies began to evaluate physicians and hospitals on control of patients' pain. Reimbursement became tied to patients' perception of pain control, further encouraging greater use of opioids.<sup>6</sup> Congress' action precipitated another change: a new DEA policy permitted physicians to issue multiple prescriptions for C-II medications during a single office visit, up to a 90-day supply.<sup>22</sup> These approaches to pain management encouraged the prescribing and supply of prescription opioids, and, inevitably, diversion.

## Questionable Claims

Prescribers saw ample support for greater utilization of opioids, but what about the risks? In 1980, the *New England Journal of Medicine* published a letter<sup>23</sup> (see **CALLOUT** above) that reported that in nearly 12,000 hospitalized patients receiving opiates for non-cancer pain, only four cases of addiction in individuals without prior addiction history were reasonably documented. The data were derived from an examination of hospital records of patients who received low dose opioids.

This widely cited and promoted reference, now considered low quality by most experts, suggested that the use of opioids for pain rarely led to addiction.<sup>23</sup> It alleviated prescriber concerns about addiction risk with long-term use of opioids. Additional reports echoed similar sentiments, concluding that opioid maintenance therapy could be a safe, humane alternative to surgery or no drug treatment for patients with intractable non-malignant pain and no history of drug abuse.<sup>12,24,24,25</sup> However, support was generalized from conclusions drawn from a specific population: inpatient, monitored individuals receiving low doses.

Vigorous promotion and marketing campaigns by opioid manufacturers further diminished reluctance to prescribe opioids due to concerns about dependence and toxicity. By the late 1990s pharmaceutical companies reassured the medical community that the risk of addiction from long-term opioids was low and prescription rates soared.<sup>12</sup> The development of potent, orally active, and long-acting opioid drugs further fueled this mindset.<sup>26</sup>

Purdue Pharma, which introduced OxyContin (oxycodone) in 1995, was a leader in this effort. OxyContin was marketed as a “less addictive opioid.”<sup>12</sup> The product’s marketing plan included reports and comments from physician-spokespersons that the opioid addiction rate was 1% and an unsubstantiated theory that drug seeking by patients with pain reflected inadequate treatment with opioids, not addiction.<sup>12</sup> In addition, patients received coupons for a free supply of OxyContin. The promotion was effective – physicians discovered a quick fix for the difficult problem of patient’s demands for relief from pain – and sales grew from \$48 million in 1996 to almost \$1.1 billion in 2000.<sup>26</sup> The phenomenon occurred despite clinical reports and the FDA’s medical review officer’s evaluation of the company’s new drug application that advised OxyContin had no significant clinical advantage over conventional, immediate-release (four doses a day) oxycodone other than a reduction in the dosing frequency.<sup>12,26</sup> OxyContin’s success correlated with increased abuse, diversion, and addiction, and by 2004 OxyContin had become a leading drug of abuse in the United States.<sup>26</sup>

### Doctor Shopping and Pill Mills

Someone had to prescribe and dispense all those prescription opioids. Doctor shopping (seeing multiple treatment providers, for the same agenda, either for treatment of a single illness episode or to obtain prescription medications illicitly) is a common means of acquiring multiple prescriptions and is a significant factor in overdose death.<sup>17</sup> A study found that the risk of overdose increased with increasing numbers of prescriptions, prescribers, and pharmacies visited, with pharmacies showing the strongest association.<sup>17</sup>

A large study analyzing prescription opioid records using data from 78% of the nation’s pharmacies found that one small subgroup of patients identified as doctor shoppers (0.7% of sample) obtained an average of 32 opioid prescriptions from 10 different prescribers over 10 months, providing them with a very high average daily dosage (109 morphine milligram equivalents [MME]) for each day of the year.<sup>27</sup> (MME is a conversion factor for comparing approximate dose equivalents of opioid drugs to a morphine standard.<sup>28</sup>) The highest probability of being in this group was age 26 to 35, the same demographic with the highest self-reported non-medical use of prescription drugs.<sup>27</sup>

Finding a willing supplier was further facilitated by the proliferation of “pill mills” (a physician, clinic, or pharmacy prescribing or dispensing drugs, usually opioids, for inappropriate or non-medical reasons) especially in Florida.<sup>29</sup> The clinics began appearing in the 1990s and blossomed in 2003. Customers arrived from distant states and were enticed by billboards on the interstate highways promising quick and easy relief from pain. By 2010, 90 of the nation’s top 100 opioid prescribers were physicians in Florida, and 85% of the nation’s oxycodone was prescribed in the state, a total of roughly 500 million doses. The number of people

## Table 1. DEA Red Flags

### Identifying Out of Scope Prescriptions

Criteria that may indicate that a prescription was not issued for a legitimate medical purpose

- The prescriber writes significantly more prescriptions (or in larger quantities) compared to other area practitioners in the same specialty.
- The prescriber writes prescriptions for antagonistic drugs, such as depressants and stimulants, at the same time.
- The patient presents prescriptions written for other people.
- A number of people appear simultaneously, or within a short time, all bearing similar prescriptions from the same physician.
- People who are not regular patrons or community residents show up with prescriptions from the same physician.
- Receiving numerous prescriptions from a physician for similar drug combinations.

### Criteria for Identifying Fraudulent (Forged) Prescriptions

- Prescription looks “too good.” The prescriber’s handwriting is too legible.
- Prescription appears to be photocopied.
- Directions are written in full with no abbreviations.
- Prescription does not comply with acceptable standard abbreviations or appears to be a textbook presentation.
- Prescription is written in different color inks or written in different handwriting.
- Quantities, directions, or dosages differ from usual medical usage.

### Patient Characteristics That Could Indicate Illegitimate Use

- The patient travels long distances to see physician or pharmacy.
- The patient uses large amounts of cash to pay for prescriptions.
- The patient appears to be returning too frequently. A prescription that should last for a month in legitimate use is being refilled on a biweekly, weekly, or even a daily basis.

dying in Florida with a prescription opioid in their system increased four-fold between 2000 and 2010 and was second only to Ohio in the number of opioid-related overdose deaths in 2017.<sup>29</sup>

## FIXING THE PROBLEM?

It was inevitable that the events described above would increase opioid availability and diversion. The severity of the opioid crisis generated efforts to decrease the prescribing and dispensing of opioids to reduce illegitimate use.

## SIDEBAR: Why carisoprodol?

Carisoprodol (N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate; N-isopropylmeprobamate, trade name Soma) is a centrally acting skeletal muscle relaxant. Its primary active metabolite is meprobamate, a substance with abuse potential similar to that of benzodiazepines.

People abuse carisoprodol for its sedative and relaxant effects, to augment or alter other drugs' effects, and by combining it with noncontrolled medications because it's relatively easy to obtain prescriptions. Its abuse became a concern in the years leading to 2010. Withdrawal symptoms include insomnia, vomiting, tremors, muscle twitching, anxiety, and ataxia. They can be pronounced in patients who abruptly cease intake of large doses of carisoprodol. Hallucinations and delusions are possible.

Several states have classified carisoprodol as a controlled substance.

'knowingly'] that the controlled substances dispensed "were likely to be diverted or used for other than legitimate medical purposes" and that "[b]y dispensing such prescriptions, [the pharmacy] failed to fulfill its corresponding responsibility for the proper dispensing of controlled substances."<sup>31</sup>

The administrative law judge who heard the DEA's complaint found that the pharmacist ignored numerous red flags when dispensing the controlled substances to these patients. He relied on testimony that the physician's patients were receiving large volumes of controlled substances in the highest strength in each prescription; receiving multiple narcotic analgesics on the same day; not receiving individualized therapy (75% of these patients received the same four drug "cocktail"); driving long distances to have their prescriptions filled; and were paying large amounts of cash for their prescriptions.<sup>31</sup>

The pharmacist maintained that the prescriber's prescriptions were valid because the physician was licensed in Ohio and the prescriptions were written for the person who presented them (i.e., they were not forged). Furthermore, he asserted that it was up to the physician to decide what and how much to prescribe and that it was "not his job to question a physician." He further stated that he did not find it suspicious that the patients were traveling long distances, paying cash, obtaining combinations of controlled substances, nor that other pharmacies had refused to fill the prescriptions.

**PAUSE AND PONDER:** Are you persuaded by the pharmacist's defense?

The administrative law judge who heard the DEA's complaint was not swayed by the pharmacist's argument and affirmed the license revocation.

## Pharmacist Responsibility

The DEA has a long-established principle that pharmacists "share a 'corresponding responsibility'" with prescribers "for the proper dispensing of controlled substances."<sup>30</sup> The DEA's Pharmacist Manual<sup>30</sup> states that a prescription that is "not issued for a legitimate medical purpose in the usual course of professional treatment ... is invalid and may not be dispensed." A person who "knowingly filling such a purported prescription" is violating the laws pertaining to controlled substances and is subject to penalties under the law. Pharmacists are required to "exercise sound professional judgment, and to adhere to professional standards, when making a determination about the legitimacy of a controlled substance prescription."<sup>30</sup> The DEA unambiguously puts the burden of the decision on the pharmacist:

"The law does not require a pharmacist to dispense a prescription of doubtful, questionable, or suspicious medical legitimacy. To the contrary, the pharmacist who deliberately ignores the high probability that a prescription was not issued for a legitimate medical purpose and fills the prescription, may be prosecuted along with the issuing practitioner, for knowingly and intentionally distributing controlled substances."<sup>30</sup>

## Red Flags

"[a] lot of pharmacists think that just because the physician wrote it, I have to fill it." Expert witness testimony from a DEA suspension order.<sup>31</sup>

Clearly, pharmacists may not robotically fill a prescription for a controlled substance but must analyze the surrounding circumstances and make a judgement call. The DEA publishes a list of criteria ("red flags") that may guide pharmacists in determining if a prescription was issued for a non-legitimate medical purpose and take appropriate steps to minimize diversion (see **Table 1**). DEA relies on these red flags in its enforcement actions. Some examples follow.

**PAUSE AND PONDER:** Did the "predicament" described above include any red flags?

In 2009, the DEA brought an action to revoke the license of a pharmacy that filled numerous prescriptions from a single physician for a combination of two opioids, a benzodiazepine, and carisoprodol (see **SIDEBAR**).<sup>31</sup> This is a common "cocktail" favored by addicts. The physician sent many of his patients to the pharmacy. The DEA deemed that these prescriptions were "issued outside the usual course of professional practice"<sup>31</sup> and therefore were not legitimate. The DEA indicated that most patients paid cash and did not live in the Columbus, OH area where the pharmacy was located. DEA's action alleged that the pharmacy "knew or should have known" [the legal standard for

In a more recent example from 2019, the DEA moved to revoke a pharmacy's license citing similar charges that the pharmacy failed to exercise its corresponding responsibility and dispensed controlled substances when it knew or should have known that the prescriptions were not for a legitimate medical purpose.<sup>32</sup> Here, the DEA cited several instances of filling prescriptions "without having first resolved the red flags of diversion." In one instance the pharmacy filled two prescriptions within a few minutes of each other for hydromorphone (Dilaudid) written by the same physician for two individuals with the same last name and street address. It also cited seven examples of new prescriptions being filled when the patients should not have finished their previous prescriptions for that drug, in some cases by as many as 15 days early. Many patients also traveled long distances (hundreds of miles in some cases) and paid in cash.<sup>32</sup>

The administrative officer hearing the case ruled that the DEA had shown that the pharmacist, "with a *subjective* belief of a high probability that controlled substance prescriptions were not legitimate and while taking deliberate actions to avoid learning of their illegitimacy, filled multiple prescriptions for controlled substances which lacked a legitimate medical purpose" (*emphasis added*). Furthermore, "when presented with a prescription clearly not issued for a legitimate medical purpose, a pharmacist may not intentionally close her eyes and thereby avoid positive knowledge of the real purpose of the prescription."<sup>32</sup> In other words, a pharmacist may not be willfully blind to the presence of red flags to avoid liability.

The ruling made another point that pharmacists need to keep in mind. The pharmacy argued that Florida law does not require documentation of red flags. However, the administrator rejected that argument, relying on "the prevailing professional standard" that pharmacists should document their resolution of red flags.<sup>32</sup>

The pharmacist also claimed that the concept of red flags stood in the way of getting medicines to deserving individuals. She testified that, "by strictly following these red flags, it will prevent legitimate patients from obtaining the medication."<sup>32</sup> (This point will be revisited in a later section.)

In a lengthy complaint filed in December 2020, the DEA criticized a pharmacy chain for abdicating its responsibility "to recognize, investigate, and resolve signs of a prescription's invalidity" (i.e., red flags).<sup>33</sup> The complaint asserted that the chain "made it difficult for its pharmacists to follow the rules" by putting "enormous pressure on pharmacists to fill prescriptions ... while at the same time denying them the authority to categorically refuse to fill prescriptions issued by prescribers the pharmacists knew were continually issuing invalid prescriptions." The complaint alleges that the chain filled prescriptions despite receiving reports from pharmacists that they came from pill mills; some prescribers were directing patients to fill their prescriptions at that chain. Managers, according to the DEA, ignored complaints from

pharmacists and pressured them to fill prescriptions as quickly as possible to shorten wait times which did not allow them an opportunity to evaluate individual prescriptions for red flags. (Management allegedly said "(w)ait times are our Achilles heel!" in response to pharmacists trying to comply with legal obligations.<sup>33</sup>) The DEA concluded that the chain failed to detect and report most of the suspicious orders that it received due to its emphasis on speed and requested civil penalties against the chain and injunctive relief.

**PAUSE AND PONDER:** Do work pressures prevent you from complying the DEA's mandate?

Sanctions for ignoring red flags are not limited to revocation of a license. In 2020, a North Carolina court ordered a pharmacy, its owner, and its pharmacist-in-charge to pay a civil penalty of more than \$1 million for filling illegitimate prescriptions for opioids and other controlled substances.<sup>34</sup> It was alleged that the defendants ignored well-known red flags of drug diversion and drug-seeking behavior for years while filling prescriptions for controlled substances. The red flags included

- dispensing "cocktails" favored by drug abusers (potent opioids plus carisoprodol or a benzodiazepine)
- repeatedly dispensing high-dose opioids for multiple family members written by a prescriber located in another state hundreds of miles away
- repeated early fills of opioids.

The chief pharmacist also allegedly often filled prescriptions his other pharmacists had previously refused to fill and ignored reports from his staff that individuals were exchanging recently dispensed drugs on the bench outside the pharmacy. Many of the store's customers died from prescription-drug overdoses within days after receiving their medications at the pharmacy. Unquestionably, it behooves pharmacy staffs to pay close attention to red flags when dispensing controlled substances.

## Guidelines

Pain management guidelines in the 1990s encouraged more aggressive treatment of pain, but as the overdose epidemic raged, new guidelines attempted to put brakes on opioid prescribing. In 2016, the CDC issued voluntary, evidence-based practice recommendations for prescribing opioids to patients 18 years or older in primary care settings, focusing on chronic pain treatment. The agency felt that there was a need for better application of guidance and standards around opioid prescribing practices. The document, *Guideline for Prescribing Opioids for Chronic Pain*,<sup>14</sup> was intended to improve pain treatment's safety and effectiveness, and reduce risks associated with long-term opioid therapy. It was a departure from the general guidelines issued two decades earlier.

One of the general recommendations is, when opioids are needed for acute pain, prescribe no more than needed and a



specific guideline is “when opioids are started, clinicians should prescribe the lowest effective dosage.” Furthermore, clinicians were urged to use caution when prescribing opioids at any dosage, carefully reassess evidence of individual benefits and risks when considering increasing dosage to 50 (MME)/day or more, and avoid increasing dosage to 90 MME/day or more.<sup>14</sup> The CDC specifically noted that the guidelines were not intended for patients in active cancer treatment, palliative care, or end-of-life care.<sup>14</sup>

In making its recommendations, the CDC considered the observation that there were inconsistent practice patterns at the county-level across the country, suggesting a lack of consensus about appropriate opioid use.<sup>35</sup> The agency acknowledged that opioid addiction rates are difficult to determine. However, it is not surprising that higher rates of opioid abuse occur in users receiving higher doses or for longer periods.<sup>14</sup> The risk of a fatal overdose rises rapidly up to prescribed doses of 200 MME/day.<sup>14</sup> The likelihood of chronic opioid use increased with each additional day of medication supplied starting with the third day in a representative sample of opioid naïve, cancer-free adults who received an opioid prescription for pain.<sup>36</sup> Large increases in the risk of chronic use were observed after five or 31 days of treatment, starting on a long-acting opioids, or a cumulative dose of 700 MME.<sup>36</sup> Many professional groups endorsed these guidelines, and they played a significant role in regulatory changes.

## Prescription Limits

Many states followed health care organizations’ lead and proposed guidelines or regulations discouraging opioid use, notably by enacting prescribing and dispensing limits. Massachusetts became the first state to pass legislation limiting opioid prescriptions in 2016.<sup>37</sup> The state set a limit of 7-days’ supply for initial (first-time) opioid prescriptions. More states followed with sev-

en states passing prescribing limits by the end of 2016.<sup>37</sup> As of August 2021, 38 states had responded to the opioid epidemic by implementing regulations or guidelines setting limits on the prescribing of opioids.<sup>38,39</sup> In five of the states, the limits only apply to Medicaid recipients.<sup>38</sup>

Most legislation limits the number of days for which a first-time opioid prescription may be prescribed. The most common maximum is seven days, but states also set limits of three, five or 14 days.<sup>37,38,39</sup> In some cases, there may be a limit on the dosage. For example, Rhode Island sets a limit of 30 MME/day for up to 20 doses.<sup>37,38</sup> Most states specify limits for acute care and make exemptions for chronic conditions, principally cancer, palliative care, long-term care, or treatment of substance use disorder. Some states may set limits on prescriptions for minors or by practice setting. For example, Pennsylvania sets a seven-day limit on prescriptions from emergency rooms, urgent care, or hospital observation, and for all minors. Alaska has a seven-day limit, but it is reduced to four days for optometrists, while Minnesota has a four-day limit for dentists. A few states provide an exemption for “provider judgment.” Several states do not have strict statutory limits but instead provide guidance or direction. For example, Maryland requires providers to prescribe the lowest effective dose for a period that does not exceed the expected duration of pain.<sup>37,38</sup>

## Changing Schedules

Another action taken was the up-scheduling of hydrocodone combination products (HCP).<sup>41</sup> Hydrocodone, without other added ingredients, became a schedule II drug upon inception of the CSA, while combination products became schedule III drugs at the same time. Typically, opiates combined with other non-opiate analgesics or used as antitussives are classified as Schedule III drugs.

**Table 2. Prescription Opioid Overdose Trends<sup>8</sup>**

Year	Any Opioid Death	Prescription Opioid Deaths	% of Opioid Deaths Attributed to Prescription Drugs
1999	8050	3442	43
2005	14918	9612	64
2010	21089	14583	69
2012	23166	14240	61
2017	47600	17029	36
2019	49860	14139	28

As the prescribing of HCPs began to spike, the DEA received many comments expressing concern from different sources including Congress and began reconsidering the placement of HCPs.<sup>41</sup> After reviewing the available data and public comments and evaluating the criteria used for determining scheduling (the “eight factor test”), the DEA concluded that the HCPs warranted placement into Schedule II. The DEA determined that this was justified because HCPs have a high potential for abuse, comparable to the Schedule II controlled substance oxycodone; abuse may lead to severe psychological or physical dependence.<sup>41</sup> Interestingly, during the public comment period, many pharmacists said that the change would increase administrative burdens and make it harder for patients to obtain their drugs, especially with the loss of refills by going to C-II. DEA published its final rule rescheduling hydrocodone combination products from C-III to C-II on August 22, 2014.<sup>41</sup>

### Prescription Drug Monitoring Programs

Prescription drug monitoring programs (PDMP), electronic databases that track the prescribing and dispensing of controlled drugs, were established in 2003 to improve opioid prescribing.<sup>42</sup> Some states mandate pharmacists to check the data base before dispensing a controlled substance.<sup>42</sup> Results have been mixed, with some states showing changes in prescribing behaviors, reduced opioid prescriptions, and slowing of opioid misuse, but the benefits have not greatly improved in aggregate.<sup>42,43</sup> However, it is worth noting that while many states implemented computerized tracking systems during the peak years of opioid prescribing, Florida did not, allowing unscrupulous pill mills to go undetected. Florida also allowed physicians and clinics to dispense the drugs they prescribed.<sup>29</sup>

### Results

Opioid prescribing rates peaked in 2010 and leveled off from 2010 to 2012, followed by a decrease of 13.1% between 2012 and 2015.<sup>13,35,43</sup> It should be noted that the drop started prior to new CDC guidelines or state prescribing limits.

A study<sup>44</sup> comparing the prescribing of opioids in January 2012 with December 2017 (more than a year after the CDC guidelines were published) found that the rate of opioid prescriptions dispensed had dropped from 6,577/100,000 persons to 4,340. Similarly, high dose opioid prescriptions (90 MME/day or more) were reduced almost in half (from 683/100000 persons to 356). Opi-

oid prescribing had decreased since its peak in 2012. However, these authors determined that after the CDC published the March 2016 guidelines, three statistics declined even faster<sup>44</sup>:

- overall opioid prescription rates
- high-dosage prescribing rates
- percentage of patients co-prescribed benzodiazepines

These changes suggest the guidelines may have had some effect in changing behavior.<sup>44</sup>

By 2019, the opioid dispensing rate had fallen to its lowest level in 14 years (46.7 prescriptions per 100 persons compared with the 2012 peak of 81.3.)<sup>43</sup> Approximately 153 million opioid prescriptions were dispensed in 2019 compared with the peak of 255 million in 2012.<sup>43,45</sup> However, prescribing remains high in some parts of the country.<sup>43</sup>

The ranking of drugs associated with overdose deaths has also changed. In 2011, the prescription drug oxycodone was the leading cause of drug overdose deaths.<sup>46</sup> Other prescription drugs (morphine and hydrocodone) also ranked high (6<sup>th</sup> and 7<sup>th</sup>, respectively). By 2016, oxycodone dropped to 6<sup>th</sup> place and hydrocodone dropped to 9<sup>th</sup> (fentanyl and heroin occupied the top two spots).<sup>46</sup>

The lethality from opioids largely paralleled the changes in dispensing. See **Table 2**. In 2010, prescription opioids accounted for almost 70% of all opioid overdose deaths.<sup>9</sup> In 2017, the number of drug overdose deaths involving prescription opioids rose to their peak, but accounted for only 36% of opioid related deaths, while by 2019, the number of prescription-opioid related deaths dropped below 2010 levels (28% of opioid deaths).<sup>9</sup>

### ARE PATIENTS THE NEW VICTIMS?

*“After being harassed by pharmacists [and] pharmacy staff for a number of years — being laughed at, being called names in front of my child — I really couldn’t take it anymore. ... They were making it really hard for me to live a pain-free life.”<sup>47</sup>*

- A California patient with pain

The policy approaches in the previous section are well-intentioned efforts to reduce controlled substance diversion. Although the decline in opioid prescribing is likely reducing diversion and overdose, some health care advocates believe the guidelines are being misapplied and have suggested that pa-



tients with legitimate prescriptions for pain are being adversely affected.<sup>21,48,49</sup>

## Pain

Chronic pain is one of the most common reasons adults seek medical care.<sup>50</sup> Studies estimate a prevalence as high as 40%.<sup>50</sup> Chronic pain has been linked to numerous physical and mental conditions including restrictions in daily activity and mobility, anxiety and depression, poor self-perception of health, and reduced quality of life.<sup>50</sup> Patients with chronic pain have an increased risk of suicide, even when controlling for other factors such as socioeconomic status, general health, and psychological disorders, and often experience a sense of hopelessness and fear.<sup>51</sup> Pain is a component of many chronic conditions and has negative consequences for society.<sup>50</sup> It is a contributing factor to high health care costs and lost productivity. Pain costs the United States an estimated \$560 to \$635 billion annually.<sup>52</sup>

## Policy Issues

A multidisciplinary expert panel, which included contributors to the CDC policy, met to review the influence of the CDC guideline's core recommendations on pain management practices. The panel concluded that some states' and professional associations' policies and practices are inconsistent with or go beyond the recommendations in the guidelines and could result in patient harm.<sup>52,53</sup> The concerns include the inflexible application of recommended dosage and duration thresholds and policies that encourage hard limits and abrupt tapering of drug dosages. The panel also noted misapplication of the recommendations to populations outside the scope of the guidelines including patients suffering from pain associated with cancer, surgical procedures, acute sickle cell crises, or treatment of opioid use disorder.<sup>52</sup>

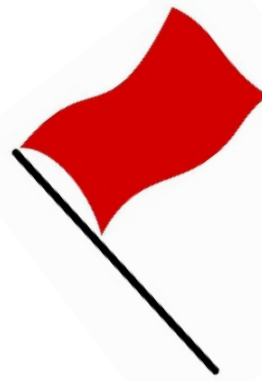
Strict application of restrictions in various guidelines have been criticized as a "one size fits all" restriction on the benefits of managing pain, and a violation of human rights.<sup>21,48,54,55</sup> Additionally, the CDC policy has been criticized for being "disproportionately focused on reducing opioid use rather than increasing pain relief" and that "excessive concerns" about the potential risks of opioid use could eliminate their use as an option for chronic pain and might deter their use of even small amounts for acute pain.<sup>52</sup> The American Medical Association is urging the CDC to make "significant" revisions to its guidelines to protect patients with pain from unintended consequences and misapplication of the guidance.<sup>54</sup>

## It Hurts to Hurt

*"It's always something and it's always some stupid excuse."*

- Comment from a frustrated 40-year-old single mom with Stage 4 metastatic breast cancer trying to fill an opioid prescription at a pharmacy<sup>56</sup>

Patients with pain have experienced difficulty receiving opioids from health care practitioners. Physicians have become leery of



regulatory oversight and risk of liability. They have reduced the dosage of opioids or completely stopped prescribing them for patients who have relied on them to manage pain safely and effectively, in some cases for decades.<sup>45,48</sup> Some providers have said that they are refusing to take new patients who were on opioids because of liability concerns.<sup>56</sup> Policies from insurers, pharmacies, and other health care organizations have invoked the CDC guidelines to limit access to opioids, in many cases contravening the guideline's recommendations.<sup>48,51</sup> When a provider's license is revoked or a pain clinic closes or is shut down, there often is no effort to ensure continuity of care resulting in patients not being tapered off their medications and suffering withdrawal.<sup>55</sup>

A survey by Human Rights Watch<sup>55</sup> found that prescribers believed they risked punishment or unwanted attention from law enforcement agencies or state medical boards if they prescribed high dose opioids, even among those prescribers who understood that the CDC guidelines were voluntary. Providers feel that they have to police themselves since the term that defines a legal prescription, acting in the usual course of their professional practice, has no commonly accepted meaning.<sup>55</sup> Human Rights Watch also surveyed patients. Nearly half of cancer patients (48%) and more than half of those with other serious illnesses (56%) said their physician indicated treatment options for their pain were limited by laws, guidelines, or insurance coverage.<sup>57</sup> Some physicians admitted reducing doses involuntarily (under fear of punitive action and without the patient's consent) for patients who were compliant with screening procedures and appeared to be benefiting from opioid therapy, often without offering alternative therapies. This practice can negatively impact a patient's quality of life, may lead to withdrawal, and can drive them to self-medicate with alcohol or illicit drugs.<sup>55</sup>

Patients being treated for pain have also complained about pharmacists who put up roadblocks when presented with an opioid prescription. Patients encounter delays or excuses, such as claims of being out of stock, or refusing to fill their prescriptions at all.<sup>56</sup> One preliminary study found that a majority of oncology patients faced difficulties in obtaining necessary opioid medications at the pharmacy and felt stigmatized as a result.<sup>57</sup>



In at least one instance, a pharmacist turned away a cancer patient, telling her that he was worried about being fined or terminated if he filled her opioid prescription.<sup>56</sup> Another patient trying to fill a prescription for opioids asked the reluctant pharmacist to contact her physician. The pharmacist replied that she did not need to call him and that the patient “should look into rehab instead of pain medication.”<sup>47</sup> In another, a cancer patient denied an opioid by a pharmacist tearfully recorded her reaction and posted the video which went viral.<sup>58</sup>

A survey performed by the American Cancer Society Cancer Action Network and the Patient Quality of Life Coalition found that the percentage of cancer survivors and patients with chronic pain taking prescription opioids is declining. Patients have faced increasing difficulty accessing opioids.<sup>57</sup> In 2018, 27% of cancer patients reported being unable to get opioid medications because pharmacists refused to fill the prescription, compared with 16% in 2016. Forty-one percent were told the pharmacy did not have the drug in stock (up from 12% in the earlier survey), while 35% of patients had a pharmacist question why they needed the medication (up from 16%).<sup>57</sup>

The difficulties do not only occur when patients try to fill prescriptions for opioid analgesics. Many patients encounter barriers when trying to fill prescriptions for buprenorphine for substance use disorder.<sup>59</sup> A 2021 survey found that 20% of pharmacies indicated that they would not dispense buprenorphine. Limited access to buprenorphine was more common among independent pharmacies and those in Southern states.<sup>59</sup>

### Red Flags or Stigma?

Many patients feel abandoned and stigmatized due to conflict with pharmacists.<sup>55,56</sup> The difficulties that patients with pain have encountered at pharmacies has led to some pushback. National class action lawsuits [lawsuits where one party collectively represents a group of people] have been filed against three of the nation’s largest pharmacy chains claiming discrimination

against patients with pain trying to fill legitimate prescriptions for opioids.<sup>55</sup> The suits allege corporate-wide discriminatory practices in refusing to fill, without a legitimate basis, valid and legal prescriptions for opioid medication.<sup>51</sup> The plaintiffs are seeking to recover damages and injunctive relief (allowing them to get their opioid prescriptions filled without delays, denial, or restrictions). The complaint asserts that “making blanket decisions regarding dispensing of controlled substances may call into question the motivation of the pharmacist and how they are using their knowledge, skill or judgment to best serve the public.”<sup>51</sup> The complaint points to patients suffering from chronic pain or pain associated with a cancer diagnosis, palliative or nursing home care, or sickle cell anemia being denied prescription opioids, which is inconsistent with the CDC recommendations. It also states that “innocent and legitimate users” are being arbitrarily treated as criminals or drug addicts and are being forced to incur unnecessary additional expenses, while suffering from debilitating pain.<sup>51</sup>

The lawsuits allege that corporate policies at the three chains encourage pharmacists to profile patients with pain as drug abusers and impose dispensing limits on opioid prescriptions.<sup>56</sup> Such policies include secret checklists listing suspicious red flags. If pharmacists are skeptical about a prescription’s legitimacy, chains advised them they were to delay dispensing.<sup>56</sup> Another chain allegedly adopted a policy limiting the supply of opioids (no more than 90 MME) for patients with acute or chronic pain and encouraged the use of immediate release formulations instead of extended release.<sup>56</sup>

In one legal action, a patient with chronic pain was told that the pharmacy would no longer fill her prescriptions for opioids. At one location, she was informed that the pharmacy had changed its policies to limit the dose and supply of opioids to comply with CDC guidelines. In another, the pharmacist on duty allegedly “screamed and yelled at her, in front of other customers, when she questioned the refusal.”<sup>51,56</sup>

In another action (against different chains), a patient is alleging a series of events took place when she tried to fill a prescription for morphine.<sup>60</sup> These include a pharmacist requiring her physician to fill out a five-page medical form and then refusing to fill the prescription because

- the “i” in morphine was not dotted
- The patient simultaneously asked to obtain naloxone
- the ICD code on the prescription was wrong

The patient also overheard the pharmacist instruct the technician to “tell that dumb bitch it won’t be ready until after midnight.”

**PAUSE AND PONDER:** What should the technician have done in this situation?

In another legal action challenging the use of red flags, a pain specialist in Kentucky successfully obtained a temporary restraining order against a pharmacy chain that refused to fill prescriptions he wrote.<sup>61</sup> He sought a judgment for tortious interference with a business relationship and defamation [a false statement to a third party that damages one's reputation]. The complaint alleges that a pharmacy representative phoned the physician and asked him questions about his medical and prescribing practices but did not inform him that any of his prescriptions were suspected of being medically unnecessary. Shortly thereafter, the chain sent him a letter announcing that its pharmacies would no longer honor his prescriptions. The physician maintains the decision was based solely on algorithms the pharmacy uses to analyze prescriber practices and did not include any review of patient records, nor evidence of a violation of law or practice. The physician also claims that the pharmacy's decision will cause his patients to suffer irreparable injury. A spokesperson for the pharmacy countered that the decision contradicts the expectation that pharmacies should use data to block some prescriptions written by prescribers and is grossly unfair to the pharmacy profession.<sup>61</sup>

## **SUMMARY AND CONCLUDING REMARKS**

"We have two public health crises going on at the same time: one is undertreated pain and the other is prescription drug abuse."<sup>1</sup> In the 1990s, there was a consensus that pain was undertreated, and opioids should be used more frequently. In the early 2010s, prescription drug overdoses exploded and there was a consensus that prescription opioids were over-prescribed. Pharmacists were cautioned about their obligation to be wary of illegitimate prescriptions. Restrictive practice guidelines and regulatory limits on opioid prescribing and dispensing became the norm. Is the pendulum swinging yet again? Recognition that many patients with pain are having difficulty accessing opioids due to measures taken by prescribers and pharmacists is growing. Pharmacists are faced with a difficult balancing act when presented with an opioid prescription.

The situation is exemplified in a brief filed by the National Association of Chain Drug Stores in a dispute between the DEA and a chain pharmacy over "suspicious orders": "Pharmacists are caught between a rock and a hard place" ... "On one hand, they may face liability if they fill facially valid physician-ordered prescriptions. On the other hand, ... they may face professional and civil liability if they refuse to fill such prescriptions."<sup>82</sup> Choose wisely.

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