



AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists and pharmacy technicians will be able to:

- Describe the historical and recent trends in the abuse of controlled substances
- Identify the types of drugs and patterns of use which increase the risk of overdose fatalities.
- Compare regulatory and public policy efforts to reduce misuse and dangers from prescription and illicit controlled substances.
- Describe the role of the pharmacist and other health professions in reducing overdose risks.



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Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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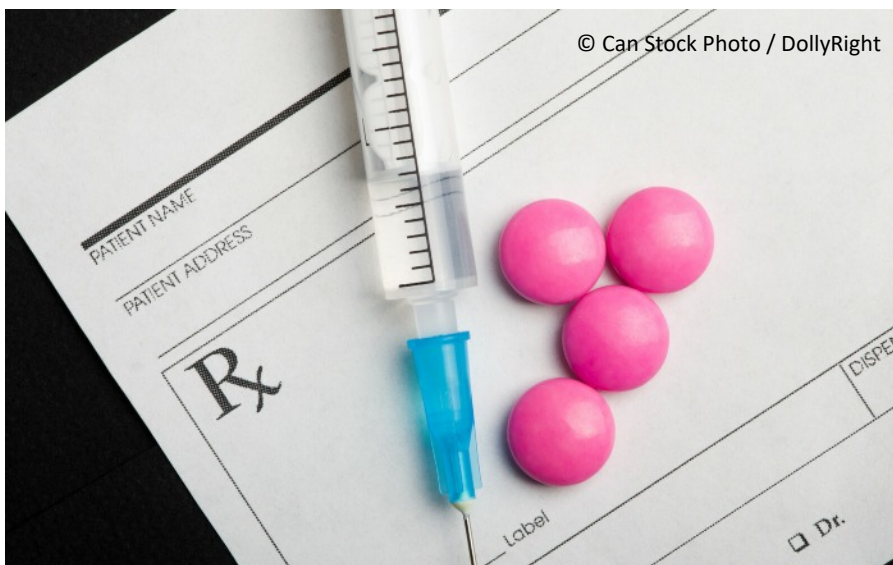
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You Asked for It! CE



Law: Connecting the Opioid Dots: Prescriptions Down, Fatalities Up

ABSTRACT: Drug overdose death rates increased almost five-fold between 1999 and 2016 and have impacted all demographic groups. Drug overdose has become the leading cause of accidental death in the U.S. and is largely fueled by opioid drugs, with other drugs also becoming significant factors. In the last decade, heroin and illicitly manufactured synthetic drugs such as fentanyl have replaced prescription opioids as the primary contributors to the overdose crisis. In response to the crisis, government and professional organizations and other policy makers have proposed a variety of solutions to the problem. This lesson will review the development of the problem and some proposed solutions that impact health care providers including addiction prevention and treatment, pain treatment guidelines, and prescribing limits on controlled substances.

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INTRODUCTION

"To every discovery mankind has ever made, from the lighting of the first fire to the splitting of the atom, there has been a good side and a bad side. Opium is no different. It can stop pain and, as Thomas Sydenham observed over 300 years ago, few doctors would be hard-hearted enough to practise medicine without it. Millions have been saved by it: yet it has also destroyed millions of lives, enslaved whole cultures and invidiously corrupted human society to its very core."¹

Readers are no doubt already aware that the "corrupted human society" forecast by British novelist and poet Martin Booth in 1999 is the occurrence of an opioid overdose crisis, which claimed 48,068 lives in 2017. The opioid crisis is the most visible segment of an overall tragedy of fatal drug overdose; total overdose deaths reached 70,237 in 2017 (up from 68,400 in the previous 12-month

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Pause and Ponder:

How many of your patients are at risk for an opioid overdose? Do you know and use the formula to predict risk routinely?

period [a 9.6% increase], 43,982 in 2013 and 17,000 in 1999).^{2,3} These alarming statistics place drug overdose as the leading cause of accidental deaths in the U.S., more than traffic accidents, AIDS at its peak, or the numbers dying during the Vietnam War.⁴

The impact of the rise in overdose deaths is so pronounced that in 2017, the life expectancy in the U.S. dropped, attributed at least in part to an increase in drug overdose and suicide. Life expectancy also declined in 2015 and stayed flat in 2016, marking the first three-year period of general decline since the late 1910s.⁵ However, the current trend is the result of more people dying in their 20s and 30s.

A problem of this magnitude is bound to attract attention from many arenas, including legislators and policy makers. In March of 2017, the President's Commission on Combating Drug Addiction and the Opioid Crisis was established to recommend policies and practices for combating drug addiction with a focus on opiates. The Commission issued a 138-page report in November of 2017, and underscored the seriousness of the issue by asking: "If a terrorist organization was killing 175 Americans a day [the average number of overdose deaths at the time the report was published] on American soil, what would we do to stop them?"⁶ The Commission made 56 recommendations in many different areas to address the growing problem.⁶ These include addiction prevention, addiction and overdose treatment and recovery, research and development (especially in pain management and addiction) and increased Federal funding. Pharmacists and technicians have seen first-hand the exacerbation and tragic consequences of the crisis. They should also ask themselves what they can do to help reduce the death toll. This lesson will focus on the scope of the drug overdose problem and review some attempts to alleviate the problem.

THE PROBLEM

Drug overdose death rates increased dramatically between 1999 and 2016.⁷ The problem has become a major source of concern; death due to drug overdose, especially opioids, has been labelled as a national epidemic,⁸ and was declared a national public health emergency by the White House in October 2017.⁹ The Centers for Disease Control and Prevention (CDC) found that overdose deaths increased in all categories of drugs examined, in men and women, people ages 15 and older, all races and ethnicities, and across all levels of urbanization.⁷ The highest rates of drug overdose deaths in 2017 occurred in adults aged 25-54, but the greatest percentage increase occurred in adults 55-64 (more than 6-fold), and in women.^{7,10}



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The largest contributor to the problem of overdose death is opioids, with two of every three overdose deaths involving an opioid or opioid mixture.⁷ The decade beginning in 2010 has been characterized by a shift in the primary driver of the opioid problem. Early in the current crisis, prescription opioids, especially diversion from legitimate sources, was the problem's principal source. More recently the blame is placed on a rise in abuse of heroin and synthetic opioids, especially illicitly manufactured fentanyls (IMFs). In 2010, more than half of opioid related deaths were due to prescription drugs, with heroin and synthetic opioids accounting for about 3000 opioid-related deaths each (14% of all opioid-related deaths for either drug).^{2,10} By 2016, 45.9% of opioid overdose deaths involved fentanyl, 40.4% involved prescription opioids, and 36.6% involved heroin (multiple causes account for a total over 100%),^{2,11} signaling a move away from prescription drugs to heroin and synthetic drugs. The rate of drug overdose deaths due to synthetic opioids increased by an average 71% per year from 2013 through 2017.^{2,10} This will be discussed further below.

While opioids dominate the number of deaths, they are not the sole problem. Central nervous system (CNS) stimulants accounted for the largest percentage increase in 2016. The cocaine-related overdose death rate increased by 52.4%, while the psychostimulant-related overdose death rate increased by 33.3%.⁷ Additionally, a recent review of National Survey on Drug Use and Health data found that between 2002 and 2016 there was a 8-fold increase in the total number of deaths involving benzodiazepines, many of which were associated with abuse of prescription opioids.²

WHY ARE OPIATES SUCH A PROBLEM?

Pharmacists and pharmacy technicians are reminded that opiates bind to different receptors, designated mu, delta, and kappa (and likely others) in the brain and other tissues.¹² The most important for the natural opiates and related opioid products are the mu receptors. Mu receptors mediate the opiates' major therapeutic actions: analgesia and decreased gastrointestinal motility. Unfortunately, they also mediate sedation, euphoria, dependence liability, and respiratory depression,¹³ so that escalating doses in an addict tolerant to the rewarding effects raises the risk of serious toxicity.¹³ Specifically, mu receptor agonists diminish the response to high levels of carbon dioxide in the medulla and also decrease the respiratory response to hypoxia. Reducing the sensitivity to the two primary drivers of respiration results in a decreased stimulus to breathe and the development of apnea and potentially death.¹³

Naloxone, a selective mu receptor antagonist, serves as a rescue drug to reverse respiratory depression and is administered by injection or as a nasal spray.¹⁴ Pharmacists in many states have prescriptive authority to dispense naloxone,¹⁵ and the expansion of naloxone availability has been a factor in reducing opioid-related overdose fatalities.¹⁶

LOOKING BACK

Rampant, deadly drug abuse is not a new phenomenon in the U.S. The current crisis represents the latest historical trend. The first national opioid crisis is generally recognized to have developed in the mid-to-late 19th century, helped along by the discoveries in the 1800s of methods to extract pure morphine from poppy, and the hypodermic syringe which facilitated drug delivery.^{6,17} With few if any effective alternatives, physicians prescribed opiates (such as morphine, laudanum, paregoric, codeine, and heroin) liberally for pain, diarrhea, cough, and a variety of other ailments. Patent medicines containing opiates were also promoted aggressively.⁸ In addition, Civil War combatants and veterans received opioid-based treatments liberally (when they weren't experiencing supply shortages) for battlefield injuries and pathogen-associated diarrhea. During this period, legal restraints that we are familiar with today were nonexistent, and now-controlled substances, including opiates and stimulants, were readily available from pharmacies and other retailers.^{6,17}

It is estimated that between 1840 and 1890, opioid consumption increased more than 5-fold¹⁷ and by 1900, one in 200 Americans was an opiate addict.⁶ Eventually, the dangers were recognized and with medical education, restraint, the advent of federal and local regulations and law enforcement efforts that prohibited treatment of addicts with opiates, and the response by physicians and pharmacists quelled the epidemic.⁶

Concerns about abuse of drugs resurfaced in the 1960s, when drugs became "symbols of youthful rebellion, social upheaval, and political dissent."¹⁸ In words reminiscent of what emanates

Pause and Ponder:

What are your state's unique abuse patterns and overdose statistics? What is your government doing to reduce overdoses?

from Washington, D.C. today, then-President Richard Nixon declared that "America's public enemy number one in the United States is drug abuse. In order to fight and defeat this enemy, it is necessary to wage a new, all-out offensive."¹⁹ The era's tactics focused on regulations and rehabilitation. One response was the establishment of the Drug Enforcement Agency (DEA) in 1973 which enforced the newly enacted (1971) Controlled Substances Act (CSA). The CSA still regulates the manufacture, sale, distribution, and possession of abused substances.²⁰ The CSA replaced more than 50 pieces of drug legislation and established for the first time a single regulatory system for both narcotic and psychotropic drugs. It also established the now familiar five schedules that classify controlled substances according to their risks, their potential for abuse and addiction, and whether they possess legitimate medical value.²⁰

The 1980s drug war saw a continuation of enforcement and a long period of a steep rise in incarceration of addicts under President Ronald Reagan, spurred by First Lady Nancy Reagan's anti-drug "Just Say No" campaign and a growing public concern over the perceived mounting illicit use of "crack."¹⁸

However, significant changes in medical attitudes towards opiates in the 1980s and 90s may have helped create the environment for the crisis that followed.

HOW DID WE GET HERE?

Abuse and diversion of prescription drugs was an early contributor to the rise in overdose deaths. The opiate prescribing accelerated rapidly in the 1980s and 90s apparently without a corresponding increase in reported pain.²¹ Between 1999 and 2002, prescriptions for oxycodone, fentanyl, and morphine increased by 50%, 150%, and 60% respectively,²² and between 1999 and 2011, oxycodone prescriptions increased 6-fold.⁴ 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.²³ National per capita consumption of oxycodone went from around 10 milligrams in 1995 to almost 250 milligrams by 2012.⁴ Prescribers wrote more than one hundred million prescriptions for hydrocodone/acetaminophen combination products alone in 2005, and it became the most prescribed drug for much of the decade.²⁴ In West Virginia, a state at the epicenter of the opioid crisis with 1.8 million residents, 780 million dose units of oxycodone and hydrocodone were dispensed between 2007 and 2012.⁴ In one community with a population of only 2,900, pharmacies processed more than 20 million opioid prescriptions over a 10-year period.⁴

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.⁶ Several factors fueled the rise in prescribing and the diversion to illegitimate use.^{6,17}

One important factor is how the medical community approached pain management. Pain was viewed as undertreated. In 1995, the American Pain Society introduced a campaign entitled "Pain is the Fifth Vital Sign" which encouraged more aggressive use of opioids for non-cancer pain.¹⁷ Similarly, the Joint Commission for the Accreditation of Healthcare Organizations, World Health Organization, and the International Organization for the Study of Pain, among others, expressed the view that pain relief was a human right.²⁵ In 2000, Congress declared 2000–2010 the Decade of Pain Control and Research, the objective of which was to recognize a new emphasis on pain management and palliative care. This initiative stated, "...physicians should not hesitate to dispense or distribute controlled substances when medically indicated."²⁵ One consequence of the shifting attitude was a change in DEA policy permitting physicians to issue multiple prescriptions during a single office visit, up to a 90-day supply, increasing the prescribing and supply of prescription opioids, many of which were inevitably diverted.

In 1980, the *New England Journal of Medicine* published a letter²⁶ in which the authors reported that in nearly 12,000 hospitalized patients receiving opiates for non-cancer pain, there were only four cases of reasonably documented addiction in individuals without prior addiction history. This widely-cited and promoted reference, now considered low quality by most experts,²⁷ suggested that use of opioids for pain rarely led to addiction. It contributed to the widespread acceptance of prescribing opiates for pain. The development of potent, orally active and long-acting opioid drugs, such as Oxycodone HCl extended release) introduced in 1995, further fueled this mindset.^{6,17}

Prior to oxycodone HCl extended release's introduction, prescribers were reluctant to prescribe chronic opioids because of concerns about addiction, tolerance, and dependence. However, the reluctance was counteracted by two actions:

- (1) opioid manufacturers' vigorous promotion and marketing campaigns, enlisting physician-spokespersons who stressed that addiction was rare, and
- (2) recognition by health care professionals that opioids were a quick fix for the difficult problem of patient's demands for relief.^{4,17}

The marked increase in opioid prescribing and the skyrocketing incidence of overdose deaths over the next two decades called for a solution.

Table 1. Representative Strategies Intended to Restrict Prescribing, Abuse/Diversion or Risks of Prescription Opiate Drugs

- Crackdown on Internet sales
- Developing abuse-deterrent formulations
- Drug testing kits
- Eliminating "pill mills" and physician dispensing
- Enhanced funding for treating substance use disorders
- Ensuring proper disposal of unused prescription drugs (e.g., "Take Back Days")
- Expanding use of prescription drug monitoring programs
- Medically supervised injection centers
- Naloxone distribution
- Pain management guidelines
- Placing limits (duration or amounts) on prescribing of opiates
- Promoting education for health care professionals about addiction and the risks posed by prescription opiates and other controlled substances
- Promoting non-opiate therapies for first-line pain control
- Promoting public education about the risks posed by prescription opiates
- Rescheduling of drugs within the DEA categories
- Syringe and needle exchange
- Urine drug testing
- Using triplicate prescription forms

RESPONSE TO THE CRISIS

Many different approaches have been recommended or implemented in response to the tragic rise in overdose-related deaths (See [Table 1](#)). A few of these that have a regulatory or other direct impact on health care professionals will be reviewed.

Rescheduling

Pharmacy staff is aware that the DEA places abused drugs into one of five categories or schedules, based upon their risks. Drugs with no accepted medical use in the U.S. are placed in Schedule I, while therapeutic agents may be Schedule II through V depending on their risks.²⁸

Traditionally, powerful opiates combined with other ingredients that would be expected to reduce abuse liability and increase analgesic efficacy (e.g., acetaminophen) or that are used as antitussives are placed into Schedule III, while the single ingredient form of the drug is placed in Schedule II. This guideline was followed for hydrocodone upon inception of the CSA in 1971. The upsurge in demand for and diversion of hydrocodone combination products (HCPs) led the DEA to upschedule HCPs to Schedule II from Schedule III in 2014.²⁸ Later, the DEA added tramadol (which was previously an unscheduled prescription drug) to Schedule IV in 2015. The effect was noticeable. Prescriptions for hydrocodone dropped in 2015, in part due to the law preventing refills for Schedule II drugs, but prescriptions for all opioids, and opioid prescription-related fatalities, had already begun falling since reaching a peak in 2010.²⁹

Treatment Guidelines

Treatment of pain poses a significant challenge to clinicians. It is estimated that 11.2% of the adult population in the U.S. experiences chronic pain.²³ Factors associated with fatalities in patients prescribed opioids include:

- using excessive doses, or initial doses that are too high for opioid naïve patients
- titrating doses too rapidly
- monitoring patients inadequately
- possessing insufficient knowledge of or using urine drug testing infrequently
- having inadequate knowledge of drug metabolism and interactions
- stratifying patients for risk suboptimally, and
- employing opioid analgesics in chronic non-cancer pain long-term.³⁰

To improve treatment and minimize the risks, several prominent organizations over the past few years have published treatment guidelines.³⁰

In 2016, the CDC issued voluntary, evidence-based practice recommendations for prescribing opioids to patients 18 years or older in primary care settings, with a focus on chronic pain treatment. Entitled *Guideline for Prescribing Opioids for Chronic Pain*,³¹ the document's purpose was to improve the safety and effectiveness of pain treatment, and to reduce the risks associated with long-term opioid therapy. The guidelines emphasized establishing treatment goals and recommended the first-line use of non-pharmacologic means (outside of active cancer, palliative, or end-of-life care). When opioids are needed for acute pain, the guidelines urge practitioners to prescribe no more than needed, stating that "When opioids are started, clinicians should prescribe the lowest effective dosage ... and should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to ≥ 90 MME/day."³¹ [MME refers to morphine milligram equivalents and is a conversion factor for comparing approximate dose equivalents of opioid drugs to a morphine standard; see page 6.³²] They also caution against using extended-release/long-acting opioids for acute pain and advise that treatment for three days or fewer will often be sufficient. As of April 2018, 46 states had implemented regulations and guidelines on prescription practices to align with the CDC recommendations. In other words, the states took the guidelines seriously.³³

Similarly, the Federation of State Medical Boards adopted a policy in April 2017 that included the recommendation that non-opioid and non-pharmacologic treatments should be considered before initiating opioid therapy.³⁴ When opi-

oids are initiated, the policy recommends that they normally be used for no more than 30 days and that there be evaluation points including improvement in pain and function.

The Centers for Medicare & Medicaid Services (CMS) has proposed an important policy change with significant impacts on pharmacists and patients; it announced that it "is deeply concerned about the magnitude of the opioid misuse epidemic and its impact on our communities, and is committed to a comprehensive and multi-pronged strategy to combat this public health emergency" by finalizing a number of new policies beginning in 2019 to "further help Medicare plan sponsors prevent and combat prescription opioid overuse."³⁵ As part of the strategy, CMS "expects" that by 2019, all Part D sponsors will limit initial opioid prescriptions for the treatment of acute pain to no more than a seven days' supply and would also limit Medicare patients to 90 mg of MME/day.³⁵ As in most policies, the CMS excludes residents of long-term care facilities; individuals in hospice care or receiving palliative or end-of-life care; or patients being treated for active cancer-related pain. CMS indicated that their actions should not impact access to medication-assisted treatment for dependent individuals, such as buprenorphine. CMS also encourages mechanisms to alert pharmacists about duplicate opioid therapy and concurrent use of opioids and benzodiazepines. These guidelines from influential health care policy makers are expected to alter prescribing practices and state regulators have taken notice.

Prescription Limits

Several states have codified the CDC's recommendations, enacting rules aligning with the CDC by placing limits on the prescribing/dispensing of opioid drugs for acute pain, effectively converting voluntary guidelines to legal mandates. The laws contain different components and state laws vary.³⁶

As of October 2018, 33 states had enacted legislation with some type of limit, guidance, or requirement related to opioid prescribing (in some states, the regulations only apply to Medicaid recipients). Massachusetts passed the nation's first law in 2016. The law contained several provisions, including setting a limit of seven-day's supply for initial (first-time) opioid prescriptions.³⁷ The most common state limit is seven days; some states apply the 7-day limit only to specific practice sites (e.g., emergency rooms, urgent care clinics).³⁶ Other states have much longer limits with a few allowing a 30-day supply, while others have more restrictive policies, some as low as three days.³⁷

Some states impose limits on the amount of drug that can be prescribed along with the durational limit. For example, Ohio and Rhode Island permit only 30 MME per day, while Maine allows 100 MME/day for a maximum of seven days.³⁶ In some states (e.g., New Jersey, New Hampshire) the limit is described as "lowest effective dose."³⁶ Maryland also uses the lowest effective dose standard but without a fixed time limit, relying on best evidence guidelines.³⁶

Technician Talk

How can pharmacy personnel tell if patients are at risk for opioid dependence?

Morphine Milligram Equivalents (MME) can be used as a guide to determine risk. An MME greater than or equal to 50 MME/Day is a concern for dependence. An MME greater than or equal to 90 MME/Day has potential overdose risks. The table to the right is a list of conversion factors provided by the CDC, which can be used to determine an MME.

Lets Do The Math: Take the dose of the drug and multiply it by the frequency, then multiply that number by the conversion factor on the chart.

Example: A patient has a prescription for oxycodone 30 mg BID.
 $30 \text{ mg} \times 2 \text{ doses} = 60 \times 1.5$ (the conversion factor in the chart)
 $= 90 \text{ MME/Day}$

This could be a concern and you should alert the pharmacist.

Download the free Opioid Guide App
www.cdc.gov/drugoverdose/prescribing/app.html

OPIOID (in mg/day unless noted)	CONVERSION FACTOR
Codeine	0.15
Fentanyl transdermal (mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
• 1-20 mg/day	4
• 21-40 mg/day	8
• 41-60 mg/day	10
• >61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3
<i>Dose conversions are estimated and cannot account for individual genetic and pharmacokinetic variations.</i>	

The medications to which these restrictions apply also vary between states. In more than half the states only opioid drugs are restricted.³⁶ Ten states include other non-opioid drugs.³⁶ All Schedule II drugs have durational limits in Illinois, Kentucky, and Missouri.³⁶ Four states expand this limitation to Schedule III and/or IV. In Tennessee, the restrictions apply to opioids and benzodiazepines, a restriction that is similar in Hawaii if the opioid and the benzodiazepine are prescribed concurrently.^{36,37} Vermont places limits depending on the level of pain; a 5-day supply for “moderate” (24 MME/day) or “severe” pain (32 MME/day), a 7-day limit for “extreme” pain (50 MME/day), and no opioid for “minor” pain (e.g., molar removal, headache, fibromyalgia).³⁸ Typically, these state restrictions do not apply to patients undergoing treatment for cancer-related pain or individuals of a long-term care facility, in hospice care, or receiving palliative or end-of-life care. Many also provide exemptions for substance use disorder or permit provider judgment.³⁷

Most states set limits on opiate prescribing in general, but some states have limits specifically for minors and may also specify other requirements, such as discussing opioid risks with the minor and parent or guardian.³⁷

For a state-by-state review of guidelines see
Opioid Prescribing Guidelines: A State-By-State Overview
(<https://www.affirmhealth.com/blog/opioid-prescribing-guidelines-a-state-by-state-overview>).

The rationale for guidelines and prescribing limits is the observation that the likelihood of long-term use and risk of overdose increases based on the duration and dose of the initial prescription. According to the CDC and other experts, the likelihood of

long-term opioid use steeply increases after the third and fifth day of dosing with an additional spike after the 31st day.^{23,29,39}

Other factors that increase the risk of long-term use include a second prescription or refill, a 700 MME cumulative dose, a long-acting opioid, an initial 10- or 30-day supply, and co-prescribing another CNS depressant.^{23,29,39} Patient factors include a history of substance use disorder, younger age, major depression, or use of psychotropics.²³ The limits have been criticized for their inflexibility which fails to address the particular needs of individual patients.³⁶

SUPPORT Act

Congress enacted The Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act in October 2018 after receiving rare bipartisan support.⁴⁰ The SUPPORT Act is a broad measure that addresses many aspects of the epidemic, including treatment, prevention, recovery, and enforcement. In particular, the Act contains provisions related to Medicaid’s role in helping states provide coverage and services to people who need substance use disorder (SUD) treatment, especially for opioids. Among its provisions, the Act requires “state Medicaid programs to have drug utilization review safety edits for opioid refills and an automated claims review process to identify refills in excess of state limits, monitor concurrent prescribing of opioids and benzodiazepines or antipsychotics, and require managed care plans to have these processes in place as of 10/1/19.” It also requires states to have Medicaid providers utilize drug monitoring programs before prescribing controlled substances and also monitor antipsychotic prescribing for children. The new law also improves access to substance use therapy and other support services.⁴⁰

BEYOND PRESCRIPTION DRUGS

Between 1999 and 2010, the rate of fatalities involving prescription opioids grew at an annual rate of 13.4% and represented the primary factor leading to overdose deaths.⁷ Lawmakers responded to these alarming statistics and sought to reduce the prescription drug supply.¹³ Some actions, in addition to those noted above, included

- expansion of prescription drug monitoring programs
- a crackdown on pill mills (a doctor's office, clinic, or health care facility that routinely conspires in the prescribing and dispensing of controlled substances outside the scope of the prevailing standards of medical practice)
- increased regulation of Internet pharmacies, and
- the reformulation of oxycodone HCl extended release.¹³

These combined efforts altered prescribing habits.³³ Prescribing of opioids peaked in 2010 at 81 prescriptions /100 people and dropped to 58/100 by 2017. High dosage (≥ 90 MME) prescriptions dropped from 11.8/100 in 2008 to 5/100 in 2017. Changes were highly variable across the country, but from 2010 to 2015, half of counties in the United States experienced reductions in the quantity of prescribed opioids. In Florida where pill-mills had proliferated, the quantity of opioids prescribed per capita decreased in 80% of counties between 2010 and 2015; during this period, Florida also experienced reductions in prescription opioid-related overdose deaths.³³

Between 2010 (prescribing peak) and 2016, fatalities involving prescription opioids increased by a much smaller annual rate of 4.8%,³ although total opioid deaths continued to exhibit a steeper rise. If prescription opioid-related deaths have slowed, why are death rates continuing to climb?

A major factor is the shift away from prescription drugs to heroin and IMF's. In late 2018, the CDC reported on the drugs most frequently implicated in overdose deaths for the period 2011-2016.⁴¹ Oxycodone ranked first in 2011 (with hydrocodone in seventh place), dropped to second in 2012 and was replaced at the top by heroin from 2012 through 2015. In 2016, the prescription drugs oxycodone and hydrocodone had dropped to sixth and ninth place, respectively, while heroin dropped to the second most involved drug, as fentanyl claimed the top spot. Cocaine consistently ranked second or third during this period. In other trends, benzodiazepines occupied two spots in the top 10 during this period while methamphetamine rose to fourth place in 2016. These three drug classes (opiates, stimulants, and benzodiazepines) comprised the top 10 for the 6-year period (See [Table 2](#)).

What factors play into the transition from prescription drugs to heroin and fentanyl? The pattern of nonmedical use of prescription opioids suggest that abuse most often starts with oral dosage forms. Once dependence is established, tolerance to

Table 2. Top 15 Drugs Involved in Overdose Deaths in 2016

Drug	Percent of Deaths
Fentanyl	28.8
Heroin	25.1
Cocaine	17.8
Methamphetamine	10.6
Alprazolam	9.8
Oxycodone	9.7
Morphine	7.9
Methadone	5.5
Hydrocodone	5
Diazepam	3.2
Diphenhydramine	3.2
Clonazepam	2.6
Gabapentin	2.4
Tramadol	2
Amphetamine	1.9

Adapted from reference 41

opioids develops and it becomes costlier to maintain abuse. Many users then employ more efficient routes of administration, such as IV injection, insufflation (nasal inhalation of recreational drugs), or smoking. Many of these users graduate to heroin, usually through contact with other drug users, sexual partners, or drug dealers, finding heroin more readily available, more potent, and more cost-effective than prescription opioids. It's also easier to manipulate (than manufactured tablets) for the preferred non-oral routes of administration.⁴²

Prescription drugs can increase the risk of opioid addiction. The rate of heroin initiation is 19 times higher in those who misused prescription drugs.⁴³ However, this does not mean that patients who were being treated for pain are the primary contributors to the rise in heroin use.^{29,43,44}

While over-prescribing of opioids has an impact on rates of addiction, evidence on how often patients being treated for pain become addicted to opiates is conflicting. A recent retrospective review found considerable variability in the rates of both opioid misuse and addiction.⁴⁵ Rates of misuse (not necessarily abuse) ranged from 2% to 56.3% and addiction rates ranged from 0.7% to 23%, with an average misuse rate of 21% to 29% and an average addiction rate of 8% to 12%.⁴⁵ Another recent meta-analysis found that the average rate of opioid dependence in patients being treated for pain was 4.7% with a range of 0.2% to 34.2%.⁴⁶ Data from the National Survey on Drug Use and Health indicates that less than 4% of people who had abused prescription opioids started using heroin within five years.⁴³ Taken together, these data suggest that prescription opioid use is only one factor leading to heroin.⁴³

Studies of patients entering treatment for heroin addiction have found that 80% had previously used prescription opioids.²¹ However, a study looking at oxycodone abuse in patients admitted to treatment centers found that 78% of patients were not prescribed the drug for any medical reason and 86% acknowledged that they acquired the drug only to “get high” not to relieve pain.⁴⁷ Many users obtained the drug from illicit sources rather than prescriptions from physicians. The authors concluded that the drug is most frequently obtained from nonmedical sources as part of a broader and longer-term pattern of multiple substance abuse.⁴⁷ Another survey of patients with various forms of SUDs found that while about half had used oxycodone, almost 90% received the drug from someone other than a prescriber, usually friends.²¹ An analysis of the sources of diverted drugs found that the most common means of obtaining prescription drugs were dealers, sharing or trading among individuals, deceiving legitimate medical practitioners, illegitimate medical practice (e.g., pill mills), and theft, in that order.⁴⁸ Similarly, another study⁴⁹ of injection drug users (largely young, white males) found that most had used opioid pain relievers nonmedically prior to using heroin, usually hydrocodone or oxycodone. The most common sources of the drugs were stealing a family member’s prescribed drug, misuse of their own prescribed opiate or, most frequently, acquiring the drug from family or friends, often in a group setting.⁴⁹ Many individuals transitioning to heroin are polydrug users.⁴³

However, it is also important to recognize that even if only a small percentage of users of prescription opioids initiate heroin, a small percentage of this very large population will inflate the number of heroin users by several hundred thousand.⁴⁸ Prescribing guidelines, prescription limits, and unscheduling are effective mechanisms to reduce the supply, diversion, and abuse of prescription opioids. However, the emphasis on reducing prescription opioids does little to prevent the abuse of heroin or IMFs and may in fact encourage their use as an alternative opioid source.⁶ The decrease in physician-generated opioid prescriptions occurred without guidelines detailing how to taper patients off the drugs and without guidance how to determine whether patients had developed an opioid use disorder, and if so, how to manage it.⁶ Consequently, patients had little support.

Some experts highlight the connection between the suppression of improper sources of prescription drugs and the subsequent rise in heroin supply and abuse. They cite the observation that heroin is a cheaper alternative to prescription drugs that is often more accessible to addicts seeking an opioid high. Patients with opioid dependence cite accessibility and price as central factors in their decision to turn to heroin.¹³ In a recent survey of people in treatment for opioid addiction, 94% indicated that they chose to use heroin because prescription opioids were becoming far more expensive and more difficult to obtain.⁴⁸

More recently, the problem has evolved to involve fentanyl and other synthetic opioids. Fentanyls are a particular concern because of their potency and their expanding distribution. Fatalities due to IMF’s increased 10-fold between 2012 and 2016.³ Fentanyl is approximately 50 to 100 times as potent as morphine and other analogs such as sufentanil and carfentanil are estimated to be 1000 and 10,000 times as potent as morphine, respectively.⁵⁰ Carfentanil detection in overdose individuals nearly doubled in 2017.⁵⁰ Coroners have detected at least 14 different fentanyl analogs as a cause of overdose deaths.⁵⁰

IMF’s are frequently added to heroin to increase its potency.²¹ Heroin users may actively seek out fentanyl-contaminated heroin to achieve a better high, while in other instances they may be unaware of the contamination.²¹ A majority of heroin users also believe that they would be able to detect contaminated heroin.²¹

While fentanyl-related deaths have increased several-fold in the past few years, it is believed that the reported numbers may under-represent the actual risk. Under-reporting is due to difficulty in detecting fentanyl analogs in overdose victims and the lack of standard inclusion in toxicology screening.⁵¹ Contamination by synthetic opioids also contributes to the rising number of deaths from other drugs. Fentanyl was a factor in 40.3% of cocaine-related overdose deaths, 31% of benzodiazepine-related overdose deaths, and 20.8% of antidepressant-related deaths in 2016.¹¹

PAUSE AND PONDER:

A prescriber discontinues opioid treatment for a 23 year old patient who has been on 70 MME of oxycodone for fibromyalgia for several months by tapering over seven days. He switches her to a combination of NSAIDs and nonpharmacologic therapies.

How might this plan influence the likelihood that the patient will seek illegal substitutes for oxycodone?

What will you tell her?

A novel approach to potentially minimizing harm from fentanyl is the use of test strips that can detect fentanyls in a liquid, analogous to a pregnancy test.⁵² The strips, which are not yet FDA-approved, can detect fentanyl and some analogs before they are injected, and several states and cities are planning on distributing them. At this time, plans for approval and distribution are not publically available, but the likelihood is that the strips will be available for people who use drugs to employ before injecting.⁵³

Fentanyls also pose a risk to first responders and other member of the public due to possible absorption from non-oral routes when they encounter individuals who have overdosed.⁵³

Fentanyl-related deaths are escalating rapidly despite the observation that fentanyl prescribing has remained steady.²⁹ Most experts^{29,51} agree that the problem does not derive from diversion of prescription products as occurred with oxycodone and hydrocodone. Instead, the fentanyl is believed to come from illicit manufacturing outside of the U.S. and smuggling, especially from China and Mexico,^{29,51} likely using the same distribution channels as heroin.⁵¹ Because of their potency, fentanyls can also be smuggled through the mail in what are called micro-shipments that are far harder to identify and interdict than the bulkier quantities of other illicit substances like heroin, cocaine, or marijuana.⁵⁴

The market for fentanyls has been characterized as a “paradigm shift.”²¹ Previously, buyers and sellers knew each other and had to maintain direct contact with sales on the street or through a loose network. Now, the new model involves a global network of largely anonymous buyers and sellers with overseas manufacturers making direct sales using global computer technology and the darknet. And, cell phones make ordering easier and improved encryption and technology make it more difficult for law enforcement.²¹ Small U.S. suppliers can purchase the substances directly from off-shore web sites and may pay using cryptocurrency. According to the DEA, a kilogram purchased for as little as \$1500 can return \$1.5 million in street sales.⁵⁴

In light of the risks in involving fentanyls, the FDA has been criticized for its recent approval of sublingual sufentanil (Dsuvia[®]) for treating acute pain in medically supervised healthcare settings.⁵⁵

Benzodiazepines are believed to be involved in almost one-third of opioid-related fatalities

Other synthetic drugs are also emerging as a problem. For example, deaths caused by U-47700 (“Pink”), a synthetic opioid originally developed by Upjohn in the 1970’s but never approved by the FDA, have been increasing.⁵⁰ Other opioid-like compounds being found in street samples include the kappa agonist U-50488, desomorphine (“Krokodil,” the street name for a homemade cheap heroin substitute used in Russia which turns the skin green and scaly with chronic use due to damage at the injection site), and tapentadol (Nucynta, with a mechanism similar to tramadol).⁶ Natural products like salvinorin A (the main psychoactive molecule from the *Salvia* plant), and its analog herkinorin have also been on the increase.⁶

Finally, benzodiazepines also contribute to the opioid overdose problem. A study found that the incidence of concurrent use of benzodiazepine and opioids increased by roughly 80% from 2001 to 2013.⁵⁶ Benzodiazepines increase the respiratory depression produced by opioids and increase risk of death.⁵⁶ Benzodiazepines are believed to be involved in almost one-third of opioid-related fatalities.^{29,56}



SUMMARY AND FINAL COMMENTS

As drug overdoses have become more commonplace and have surpassed other causes of accidental death in the U.S., attention has been focused on seeking ways to lessen the problem (See [Table 1](#)). Proposed solutions impact all health care providers. They include changes in pain management, enhanced monitoring and restriction of prescribing and dispensing, providing rescue naloxone and other methods to mitigate overdosing, improved public education, and better treatment of substance use disorder.

What can pharmacy staff do? Although prescribing of opioids has declined, prescription drugs are still an important source of fatalities and pharmacists need to continue to play an active role in preventing diversion of controlled substances while also improving pain management. Pharmacists need to be mindful of these two potentially conflicting goals. When it comes to diversion of prescription drugs, pharmacists are reminded that they have a shared legal responsibility with prescribers to prevent abuse.⁵⁷ The CSA states that a prescription for a controlled substance must only be issued for a “legitimate Medical purpose.” Furthermore, while the responsibility for prescribing rests with the prescriber, there is a “corresponding responsibility” for the pharmacist who fills the prescription. The DEA points out that the “person” who knowingly fills an invalid prescription is subject to penalties. As such, a pharmacist must exercise “sound professional judgment” when determining the legitimacy of a prescription. A pharmacist is not required to dispense a prescription of “doubtful, questionable or suspicious origin”⁵⁷ and should not feel compelled to do so. The President’s Commission⁶ has further recommended that regulatory bodies and pharmacy associations train pharmacists on best practices to evaluate the legitimacy of opioid prescriptions, and not penalize pharmacists for denying inappropriate prescriptions.

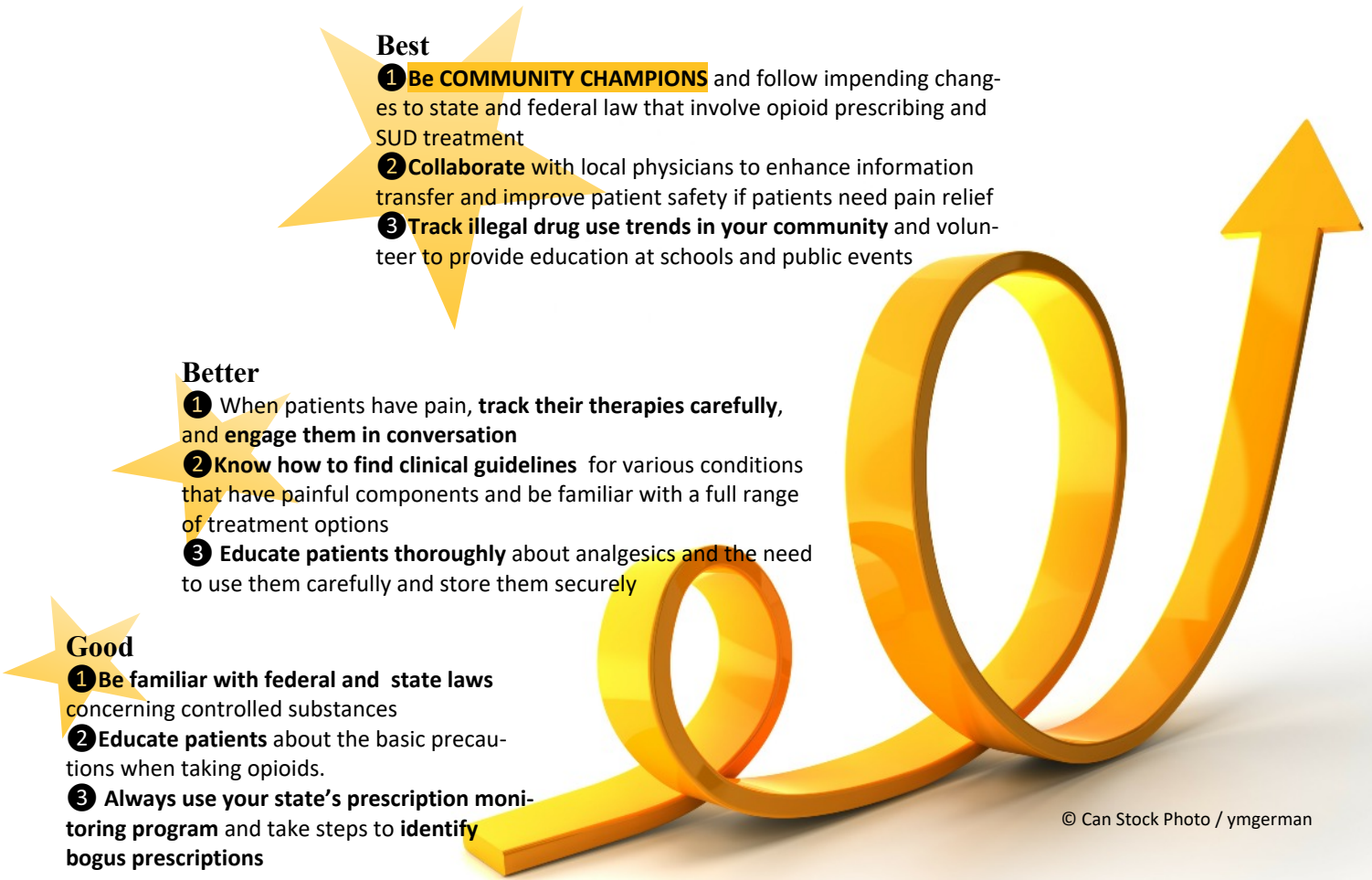
While pharmacists should continue to take steps to help reduce the unnecessary prescribing of powerful analgesics, they should also recognize that the drug overdose problem goes far beyond prescription opioids. Heroin and the illegally manufactured fentanyl have passed prescription drugs as factors responsible for overdose deaths and the tightening of controls on prescription drugs may be contributing to the surge in their use. In addition, CNS stimulants are now the fastest growing segment of overdose deaths in the U.S. , while drugs such as gabapentin, tramadol, and benzodiazepines are becoming more of a concern.³⁹

At the same time, patients with legitimate pain issues are finding barriers to accessing effective treatment.^{29,58,59} It is estimated that 10% to 20% of U.S. adults (about 50 million people) suffer with chronic pain, with 8% having high impact pain defined as pain lasting at least three months associated with one major activity restriction (e.g., being unable to work, attend school, or do household chores).⁵⁸ The economic cost of chronic pain due to medical expenses, lost productivity, and disability programs is estimated to be \$560 billion/year.⁵⁸ Pain also has a major impact on mortality, health, and the quality of psychological and social life, including an increased risk of depression and suicide.²⁹

Despite these needs, patients report increasing numbers of practitioners refusing to write prescriptions for opioids, and pharmacies refusing to fill prescriptions. Patients also report facing hostile reactions and stigma from pharmacists.^{29,59}

Significantly, patients report that mixed messages in the media and from practitioners leads to confusion and misunderstandings about the drugs and the nature of addiction, even in cancer patients,⁵⁹ a niche that pharmacists should be able and willing to help. The President’s Commission includes among its recommendations additional efforts to improve health care practitioners’ awareness.⁶ It recommends that governmental entities move to allow the DEA to require that all health care practitioners desiring to be relicensed to prescribe opioids participate in an approved continuing medical education program on opioid prescribing. At least 23 states already require practitioners to obtain continuing education credits in one or more of the following: prescribing controlled substances, pain management, and identifying substance use disorders.³⁷ Pharmacists should embrace the opportunity to become better informed and make the public aware of Booth’s message that “millions have been saved by (opium) yet it has also destroyed millions of lives.”¹

Figure 1. Advancing Pharmacists and Pharmacy Technicians Role in Stemming Opioid Overdose



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