Prescription Opioids: Risk Management and Strategies for Safe Use

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, physician assistants, nurses, and pharmacy professionals involved in the care of patients prescribed opioids to treat pain.

Accreditations & Approvals

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Course Objective

The purpose of this course is to provide the information necessary for clinicians to make informed decisions regarding prescribed opioids in order to minimize adverse events, substance abuse, and drug diversion.

Learning Objectives

Upon completion of this course, you should be able to:

1. Define terms associated with opioid therapy and aberrant drug use.
2. Analyze behavioral responses to prescribed opioids and signs of emerging opioid misuse.
3. Outline the impact of clinical and professional society attitudes toward opioid prescribing.

4. Review the role of OxyContin in the rise of prescribed opioids for chronic noncancer pain.
5. Evaluate the basic epidemiology of prescription opioid use, misuse, and dependence in the United States.
6. Identify factors that influence opioid prescribing decisions.
7. Describe the morbidity and mortality associated with the use of prescription opioids.
8. Discuss characteristics of appropriate and inappropriate opioid prescribing and contributory factors to both.
9. Compare opioid abuse risk assessment tools and the utility of risk stratification.
10. Outline the appropriate periodic review and monitoring of patients prescribed opioid analgesics, including the role of urine drug testing.
11. Describe necessary components of patient/caregiver education for prescribed opioid analgesics, including guidance on the safe use and disposal of medications.
12. Compare available opioid abuse-deterrent formulations.
13. Evaluate government and industry efforts to address problems arising from prescription opioid analgesic misuse.
14. Review the unintended negative consequences of efforts to reduce prescribed opioid analgesic misuse, diversion, and overdose.
15. Discuss treatment considerations for patients with active or remitted substance use disorder who require prescribed opioid analgesics for chronic pain.

Pharmacy Technician Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the background, definitions, and epidemiology of opioid use and prescribing.
2. Describe components of an appropriate opioid prescribing program.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

In the United States, the use of prescription opioids for the treatment of pain is challenging and complex. There exists a prevailing tendency to inappropriate patterns of underprescribing (because of fear of adverse effects and addiction) or overprescribing (because of failure to select properly or frustration over a poor therapeutic response). These practice patterns are especially prevalent in the management of patients with chronic noncancer pain and have resulted in or contributed to unnecessary patient suffering from inadequately treated pain and increasing rates of opioid abuse, addiction, diversion, and overdose.

Morphine was synthesized close to 200 years ago and entered clinical use more than 150 years ago. To this day, morphine and its opioid analogs remain the most powerful analgesics for severe acute pain and effective therapies for many chronic pain conditions. Opioid analgesic prescribing for pain control has risen dramatically since the late 1990s, and although opioid analgesic use in moderate-to-severe acute pain, cancer pain, and terminal pain is widely accepted, its use in chronic noncancer pain remains controversial [1]. Opioids can provide effective pain control, but problematic side effects are common, long-term outcomes vary, and escalating rates of addiction, diversion, and fatal overdose involving opioids have occurred in tandem with their increasing clinical use for pain control. These negative outcomes from increasingly widespread prescribing have heightened awareness of the need for prescribers to mitigate the inherent risks that come with opioid analgesics in order to minimize their abuse, addiction, diversion, and fatal toxicity [2].

There is a shortage of pain specialist physicians in the United States that is expected to worsen, and this has resulted in most of the medical care for patients with chronic pain being delivered by primary care physicians [3]. The current problems involving prescription opioid analgesics are primarily the result of prescriber factors and the undue

influence of stakeholders over pain medicine practice [4; 5]. Prescriber factors include inappropriate opioid prescribing and inadequate patient counseling and monitoring, reflecting deficits in knowledge, competence, and performance [6]. Many primary care providers lack sufficient knowledge or training in pain medicine and in appropriate opioid use, and the majority report they do not feel confident managing chronic pain [7; 8]. A clinical skills assessment by the American Academy of Family Physicians found significant and widespread knowledge deficits among family practice physicians in the medical skills necessary for providing optimal pain management, managing drug abuse and addiction, and utilizing risk evaluation and mitigation strategies when prescribing opioids [9].

The goal of this course is provide clinicians with an understanding of the essential components of appropriate opioid prescribing. This objective will be achieved through discussion of behavioral responses in patients receiving opioids for pain; the antecedents, catalysts, manifestations, and consequences of the dramatic and widespread increase in clinical and illicit use of prescription opioids; the assessment and management of pain; patient risk of developing problems with their prescribed opioid analgesic; governmental, law enforcement, and industry strategies and tactics to reduce prescription opioid abuse; and treatment approaches for patients with comorbid chronic pain and substance use disorders. Among primary care providers, there is great variability in the understanding of opioid use and misuse and in the confidence with which opioids are used for management of chronic pain. Often, there is confusion or difficulty distinguishing physiological tolerance and dependence or uncontrolled pain behaviors from symptoms and signs of opioid use disorder. In addition to substantial differences in patient tolerability and analgesia with opioid analgesics, patients can also exhibit a range of psychological, emotional, and behavioral responses to prescribed opioids, the result of inadequate pain control, an emerging opioid use problem, or both. An appreciation for the complexities of opioid prescribing, and the dual risks of litigation due to inadequate pain control and drug diversion or misuse, is necessary for all clinicians in order to provide the best possible patient care and to prevent a growing social problem.

There is also considerable evidence that, in the past, major stakeholders have negatively influenced the delivery of safe, effective, and appropriate analgesic care to patients with chronic pain. This has occurred, in part, through bias of the information provided to clinicians to guide their practice and prescribing behavior with respect to opioid analgesics. Effective practice is based on training, clinical judgment, and ongoing study of advances in practice areas. Careful clinicians pay attention to published research and other mediums of knowledge transfer that are relevant to their particular practice, with a trained eye toward the quality of evidence. Unfortunately, much of what has been published on chronic pain management, especially as regards opioid drug use, has uncertain validity because of various forms of bias and nonrigorous statistical analysis. This has had an adverse impact on the consistency and quality of care, on clinician confidence in how to render care, and on the public health cost of opioid analgesic care. For these reasons, an ***Appendix*** to this course has been included to provide some historical perspective on opioid prescribing practices and to address sources of bias in clinical (therapeutic) research.

DEFINITIONS

Definitions and use of terms describing opioid analgesic misuse, abuse, and addiction have changed over time, and their current correct use is inconsistent not only among healthcare providers, but also among federal agencies reporting epidemiological data such as prevalence of opioid analgesic misuse, abuse, or addiction. Misuse and misunderstanding of these concepts and their correct definitions has resulted in misinformation and represents an impediment to proper patient care.

OPIOID ABUSE, DEPENDENCE, AND ADDICTION

Inappropriate opioid analgesic prescribing for pain is defined as the nonprescribing, inadequate prescribing, excessive prescribing, or continued prescribing despite evidence of ineffectiveness [10]. Appropriate opioid prescribing is essential to achieve pain control, to minimize societal harms from diversion, and to minimize patient risk of abuse, addiction, and fatal toxicity. The foundation of appropriate opioid prescribing is based on thorough patient assessment, treatment planning, and follow-up and monitoring. Essential for proper patient assessment and treatment planning is comprehension of the clinical concepts of opioid abuse and addiction, their behavioral manifestations in patients with pain, and how these potentially problematic behavioral responses to opioids both resemble and differ from physical dependence and pseudodependence. Prescriber knowledge deficit has been identified as a key obstacle to appropriate opioid prescribing and, along with gaps in policy, treatment, attitudes, and research, contributes to widespread inadequate treatment of pain [7]. A 2013 survey measured primary care physician understanding of opioids and addiction. Of the 200 participants, [11]:

- 35% admitted knowing little about opioid addiction.
- 66% and 57% viewed low levels of education and income, respectively, as causal or highly contributory to opioid addiction.
- 30% believed opioid addiction "is more of a psychological problem," akin to poor lifestyle choices rather than a chronic illness or disease.
- 92% associated prescription analgesics with opioid addiction, but only 69% associated heroin with opioid addiction.
- 43% regarded opioid dependence and addiction as synonymous.

This last point is very important because confusion and conflation of the clinical concepts of dependence and addiction has led to accusations of many nonaddicted patients with chronic pain misusing or abusing prescribed opioids and to failure to detect treatment-emergent opioid problems [12]. Knowledge gaps concerning opioid analgesics, addiction, and pain may be related to attitude gaps, and negative attitudes may interfere with appropriate prescribing of opioid analgesics. For example, when 248 primary care physician survey participants were questioned regarding their prescribing approach in patients with headache pain and either a past or current history of substance abuse, 16% and 42% of physicians, respectively, would not prescribe opioids under any circumstance [13]. Possibly contributing to this knowledge deficit is the extent of educational exposure to concepts central in pain management.

A 2018 systematic review evaluated pain medicine curricula in 383 medical schools in Australia, New Zealand, the United States, Canada, the United Kingdom, and Europe [14]. Pain medicine was primarily incorporated into anesthesia or pharmacology courses, rather than offered as a dedicated pain medicine module. Ninety-six percent of medical schools in the United Kingdom and the United States and nearly 80% of medical schools in Europe had no compulsory dedicated pain medicine education. The median number of hours of pain content in the entire medical school curriculum was 20 in Canada, 20 in Australia and New Zealand, 13 in the United Kingdom, 12 in Europe, and 11 in the United States [14].

The nomenclature related to addiction is often inconsistent, inaccurate, and confusing, partially reflecting the diverse perspectives of those working in the related fields of health care, law enforcement, regulatory agencies, and reimbursement/payer organizations. Changes over time in the fundamental understanding of addiction have also contributed to the persistent misuse of obsolete terminology [15]. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM), published by the American Psychiatric Association, is perhaps the most influential reference for the diagnosis of addiction and all other psychiatric disorders.

OPIOID USE TERMINOLOGY	
Term	**Definition**
Misuse, nonmedical use	Use of the opioid that departs from intended prescribing by the provider
Abuse	A maladaptive pattern of opioid use with the primary intent of achieving euphoria or getting high
Addiction	A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. Characterized by behavior including impaired control over drug use, compulsive drug use, continued use despite harm, and drug craving.
Physical dependence	The expected response to chronic administration of many drug classes such as opioids, anabolic steroids, and beta-blockers, manifesting in neurologic adaptation whereby a drug class-specific withdrawal syndrome is produced by abrupt cessation, rapid dose reduction, decreased blood concentration, or antagonist administration
Tolerance	A state of adaptation in which the physiologic changes from drug exposure over time lead to diminished drug effect
Pseudoaddiction	An iatrogenic condition whereby patients display aberrant drug-seeking behaviors mimicking opioid use disorder but driven by intense need for pain relief. Resolves with adequate pain relief.
Diversion	Transfer of a controlled substance from authorized to unauthorized possession or distribution
Opioid	Any compound that binds to an opioid receptor in the CNS, including naturally occurring, synthetic, and semi-synthetic opioid drugs and endogenous opioid peptides
Iatrogenic	A response, usually unfavorable, to a medical or surgical treatment induced by the treatment itself
CNS = central nervous system.	
Source: [10; 20; 21]	*Table 1*

Prior to the 2013 release of the DSM-5, previous versions eschewed the term "addiction" in favor of "substance dependence," with a separate diagnostic entity of "substance abuse" representing a lower-grade, less severe version of substance dependence [16]. Also in earlier DSM versions, physiological dependence, manifesting as substance tolerance and withdrawal, was considered a diagnostic criterion of substance dependence. The result was the perpetuation of patient and healthcare professional confusion between physical and psychological dependence and the belief that tolerance and withdrawal meant addiction. This confusion enhanced provider and patient fears over addiction developing from opioid analgesics and contributed to the undertreatment of pain [16]. The DSM-5 has eliminated the categories of substance dependence and substance abuse by combining them into the single diagnostic entity of substance use disorder. The disorder is measured on a continuum from mild to severe [16].

In 2011, the American Society of Addiction Medicine (ASAM) published their latest revision in defining the disease of addiction. Since that time, the public understanding and acceptance of addiction as a chronic brain disease and the possibility of remission and recovery have increased. Additionally, there is growing acknowledgment of the roles of prevention and harm reduction along the spectrum of addiction and recovery. Consequently, ASAM updated its definition of addiction and adopted the following revised definition in 2019 [17]:

> Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases.

COMMON MISCONCEPTIONS OF PAIN THERAPY WITH OPIOID ANALGESICS AND ADDICTION	
Misconception or Belief	**Correction**
The tolerance and withdrawal of opioid dependence equates to opioid addiction.	Tolerance, withdrawal, and physiologic dependence are expected responses to opioids and other controlled substances when given in sufficient doses over time and are not, by themselves, indicative of addiction.
Addiction can be accurately predicted and diagnosed in the initial assessment of patients with pain.	Addiction is not an entirely predictable response to reward-producing drugs but may occur in biologically and psychologically susceptible individuals; it is diagnosed over time based on established criteria.
Medications for pain or anxiety should not be used in patients with a substance use disorder history.	Uncontrolled pain or anxiety and other psychiatric illnesses may trigger a relapse to substance use or exacerbate an existing disorder. Treatment should be tailored to patient need and may include alternative treatment modalities, monitored prescriptions, or other measures as needed.
Behaviors such as "clock-watching," preoccupation with obtaining opioid analgesics, deception, stockpiling unused medication, and illicit substance use indicate addiction.	Patients with undertreated pain may engage in problematic behaviors that mimic opioid abuse but are driven by intense need for relief and resolve with adequate pain control.
Substance misuse is the same as substance abuse, dependence, or addiction; all require cessation of opioid prescribing.	Many factors can underlie substance misuse, including varying cultural values, lack of education, misunderstandings, and poor judgment, that do not meet the criteria for a substance use disorder. Misuse does require evaluation for patient education and possible treatment modifications but does not mandate discontinuation of opioids.
Opioid therapy always leads to addiction.	This has been proven false; the rate of iatrogenic opioid use disorder is low.
Some opioids are worse than others in terms of addiction potential.	Addiction is the result of individual susceptibility, and any opioid analgesic can be abused by predisposed individuals.
If morphine is used now, there will not be options when the pain worsens.	An increase in pain severity can be countered by dose increase, switching to another opioid, or adding a non-opioid analgesic.
If I start taking an opioid, I will have to keep increasing the dose to control my pain.	After an effective dose is reached, many patients with chronic pain are able to maintain analgesia on the same dose.
Morphine and opioids cause heavy sedation and probably hasten death.	The initial sedation goes away within the first two weeks of initiation. Opioids have conclusively been shown to not hasten death in hospice patients; pain undertreatment is a far greater concern in hastening death.
Source: [15; 21]	*Table 2*

According to the ASAM, the five characteristics of addiction are [18]:

- Inability to consistently abstain
- Impairment in behavioral control
- Craving or increased "hunger" for drug or reward experiences
- Diminished recognition of significant problems with one's behaviors and interpersonal relationships
- A dysfunctional emotional response

TERMS TO AVOID OR LIMIT THE USE OF	
Term	**Rationale for not using**
Addicted/addiction	Frequently misused by those untrained to make the diagnosis. Not all who abuse are addicted.
Addictive	Patently false when describing a substance. Addiction resides within the person and not in the substance used. Some drugs do have high abuse liability, but most persons do not respond to exposure with addictive behavior.
Chemical coping	Overused in the literature and by clinicians. Not very helpful, especially if a better treatment or coping strategy is not immediately available.
Drug-seeking	Used when a patient is assumed to lack legitimate need for medication. Should be replaced with relief-seeking, if appropriate.
Hooked	Slang for addicted. Assumes the absence of medical need for the substance and suggests an off-hand, bad attitude.
Inebriated/intoxicated	A snap conclusion when a patient suspected of taking medication or other substance displays an altered sensorium. Better to objectively describe observations.
Malingering	Overcalled and best not expressed unless there is legally valid proof of deception for illicit purposes.
Narcotic	A term formerly referring to opium, morphine, and heroin and still used in the area of law and misused by media in reference to all opioids. Should never be used in a clinical or education context due to strong emotional association with crime, addiction, and death. Best replaced with opioid.
Painkiller	Negative use by media in reports of opioid addiction and overdose. Best replaced with pain reliever.
Source: [19; 22]	*Table 3*

This summary of addiction should not be used as diagnostic criteria for addiction because the core symptoms vary substantially among addicted persons, with some features more prominent than others [17].

Many terms used in discussions of opioid use and misuse may have ambiguous meanings (***Table 1***). The absence of consensus in the terminology and definitions of substance use, substance use disorders, and addiction has led to considerable confusion and misconceptions (***Table 2***). These misconceptions may be harbored by clinicians, patients, family members, and the public and can negatively impact patient interaction, assessment, treatment, and outcomes. Correction of these erroneous beliefs and attitudes is important, as is the use of nonpejorative and nonstigmatizing language when describing opioid analgesics, the patients who need them, and patients who develop aberrant behaviors or addiction involving opioids (***Table 3***). Pejorative terminology has a strong negative effect on patients and serves to reinforce their sense of shame and stigma over using opioid analgesics. These terms signal a negative attitude and judgment to patients [15; 19].

BEHAVIORAL RESPONSES TO PRESCRIBED OPIOIDS

Patients with pain display a continuum of behavioral responses to prescribed opioids. Some develop aberrant behaviors, which are defined as unintended behaviors involving the acquisition or use of prescribed opioids [23]. Depending on the study, researchers have reported that as many as 40% of patients with pain receiving opioid therapy exhibit aberrant behavior; however, in only a minority of these patients does the aberrant behavior reflect

CONSIDERATIONS FOR DIFFERENTIAL DIAGNOSES
• Inadequate pain management: – Stable condition but inadequate pain control – Progressive condition/pathology – Tolerance to opioids • Inability to comply with treatment due to: – Cognitive impairment – Psychiatric condition • Self-medication of mood, anxiety, sleep, post-traumatic stress disorder, etc. • Diversion
Source: [19; 22] *Table 4*

an emerging opioid use disorder. It is important to distinguish the underlying basis and the level of risk for opioid use disorder represented in the aberrant behavior. This is accomplished by differential diagnosis (***Table 4***). To capture the perspective of pain practitioner viewpoints in associating aberrant behaviors and risk of patient opioid problems, 100 pain physicians were instructed to rank a list of 13 aberrant drug-use behaviors from least to most suggestive of emergent opioid use disorder. Selling the prescribed opioid and prescription forgery received highest ranking as most aberrant, and altered route of administration was given the third highest ranking. Lowest ranked were unkempt patient appearance, sporadic unsanctioned dose escalation, and prescribed opioid hoarding [24].

There are certain behaviors that are suggestive of an emerging opioid use disorder. The most suggestive behaviors are [25; 26; 27]:

- Selling medications
- Prescription forgery or alteration
- Injecting medications meant for oral use
- Obtaining medications from nonmedical sources
- Resisting medication change despite worsening function or significant negative effects
- Loss of control over alcohol use
- Using illegal drugs or non-prescribed controlled substances
- Recurrent episodes of:
  - Prescription loss or theft
  - Obtaining opioids from other providers in violation of a treatment agreement
  - Unsanctioned dose escalation
  - Running out of medication and requesting early refills

Behaviors with a lower level of evidence for their association with opioid misuse include [25; 26; 27]:

- Aggressive demands for more drug
- Asking for specific medications
- Stockpiling medications during times when pain is less severe
- Using pain medications to treat other symptoms
- Reluctance to decrease opioid dosing once stable
- In the earlier stages of treatment:
  - Increasing medication dosing without provider permission
  - Obtaining prescriptions from sources other than the pain provider
  - Sharing or borrowing similar medications from friends/family

It is essential for clinicians to consider poorly managed pain or poor coping skills as the basis for aberrant behavior. Even aberrant behaviors highly suggesting opioid abuse may reflect a patient's attempt to feel normal or alleviate emotional or physical distress. This is termed chemical coping and refers to the inappropriate use of a prescribed opioid to treat emotional or psychiatric conditions, commonly depression, anxiety, and insomnia. In these cases, the patient is not technically addicted to the opioid, but he or she fears withdrawal from the opioid and losing the ability to function without the drug and, as a result, may abuse opioids, engage in illegal behavior to obtain opioids, or doctor-shop. Aberrant behavior can also be driven by undertreated pain or a failure of treatment man-

agement [28]. Importantly, no single behavioral marker clearly identifies addiction in patients with pain who are prescribed opioids, and while all addicts are abusers, not all abusers are opioid-addicted [28].

For the purposes of this course, the term opioid addiction is used to indicate a severe opioid use problem, consistent with the definition of addiction provided earlier in this course and in place of the now-discarded DSM-IV term of opioid dependence. Opioid use disorder is used to encompass the range of problematic opioid use.

CLINICIAN AND PROFESSIONAL SOCIETY ATTITUDES TOWARD OPIOID PRESCRIPTION DRUG USE

BACKGROUND

Opium and its alkaloids have been used for thousands of years as analgesics. From the end of the 19th century into the early 20th century, heroin was sold as a cough suppressant and briefly promoted as more effective and less addictive than morphine. It was legally marketed in pill form and became widely abused for the intense euphoria by crushing the heroin pills into powder for inhalation or injection [1]. Heroin addiction skyrocketed, and Congress banned the drug in 1924. Wariness of prescribing opioids persisted through the 1980s and 1990s [29].

The United States has a long history of pain undertreatment as a standard medical practice. This was a consequence of the long-standing emphasis on treating the underlying primary illness, minimizing the importance of addressing pain, and viewing pain as an endurable consequence [1]. Another primary factor historically responsible for pain undertreatment has been a resistance to prescribing opioids, driven by fears of patient addiction and the threat of prosecution and potential loss of licensure if opioid prescribing was deemed inappropriate by the state medical board. The widespread practice of including non-professional lay members on medical boards intensified physician concerns over prejudicial interpretation by board members, even when legitimate medical necessity merited long-term, high-dose opioid prescribing to patients with severe, chronic noncancer pain [29].

These physician concerns were confirmed by the results of a 1992 survey that captured medical board member perception and opinion of legality and appropriateness in opioid prescribing for different pain conditions. A total of 304 members of 49 state medical boards were surveyed; 85% were physicians (MDs and DOs) and 15% were lay public members [30]. Physician members were asked to rank 12 opioids by their order of recommendation for chronic, moderate-to-severe cancer pain. The top selection was codeine with aspirin/acetaminophen (47%), despite codeine being widely accepted as too weak for chronic moderate-to-severe pain. When asked of the general incidence of psychological dependence (as compulsive nonmedical use) from opioid pain treatment, 39% did not know. When asked to define "addiction" by selecting one or more of several common definitions, 85% chose physical dependence, 71% chose psychological dependence, 41% chose tolerance, 21% chose physical dependence alone, 10% chose psychological dependence alone, and 1% chose tolerance alone [30].

Respondents were also asked for their opinion, as state medical board members, of the legality and medical legitimacy of opioid prescribing longer than three months for several patient scenarios. Approximately 10% of board members described opioid prescribing as illegal under medical practice, controlled substances law, or both, and requiring investigation in patients with cancer pain alone, 26% in cancer pain with patient history of opioid abuse, 59% in chronic noncancer pain alone, and more than 90% in patients with chronic noncancer pain and history of opioid abuse [30]. Underscoring the gravity of these findings was that 80% of respondents stated their medical board was the agency most likely to investigate improper controlled substance prescribing in their state [30].

Against this backdrop, some pain physicians began to re-examine and challenge the intense physician reluctance to prescribe opioids. Observing the extent that suffering was relieved by opioids in cancer patients with severe pain and the apparent lack of euphoria that differed from the responses of opioid abusers, it was suggested that opioids could also be used to relieve suffering in many patients with intense, persistent noncancer pain, with little risk of addiction. This was followed by an effort to destigmatize the use of opioids, with the objective of easing access to opioids by the large number of patients with severe, persistent noncancer pain. While widely viewed as driven by good intentions, this crusade for acceptance of opioid use in noncancer pain was also accompanied by the regular tendency to minimize the inherent potential risks that accompany opioid prescription drug use, despite the absence of valid evidence to support the assumption [31].

Results from a 1986 chart review study of 38 patients with chronic noncancer pain receiving long-term opioid therapy were cited to support the assertion that long-term opioid use in patients with intractable nonmalignant pain was effective and safe with little risk of addiction. Of the 38 patients in the study, the 2 who developed opioid problems had histories of drug abuse [32]. This paper was followed by several other publications on opioids for chronic noncancer pain [33; 34; 35; 36]. Each paper cited the prevalence rates of iatrogenic opioid addiction reported by three earlier pain studies [37; 38; 39]:

- Of 11,882 hospitalized patients with a negative substance abuse history who received ≥1 opioid dose, 4 developed addiction.
- A national survey of roughly 10,000 patients treated for burn pain found no cases of addiction.
- Of 2,369 patients treated at a headache center who had access to opioid analgesics, 3 developed problems with their prescribed opioid.

These iatrogenic addiction figures were disseminated through communications to specialists, general practitioners, other providers, administrators, regulators, and the lay public. "Less than 1%" became the message that opioids posed little risk of addiction in patient with pain without substance abuse histories. Substantial support for compassion-based efforts to broaden opioid use for pain control also came from the 1990 opinion paper by the co-author of the landmark paper describing gate control theory that revolutionized the concept of pain [40]. In 1988, the Federation of State Medical Boards (FSMB) released a policy explicitly reassuring physicians they would not face regulatory action for prescribing even large amounts of opioids, assuming it was medically warranted [31]. Physician awareness of the new FSMB policy was promoted by widely circulated publications. For example, the Joint Commission published a guide, supported by Purdue Pharma, stating, "Some clinicians have inaccurate and exaggerated concerns about addiction, tolerance, and risk of death," and "This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control" [31].

During the 1990s, the American Pain Foundation endorsed more aggressive treatment of chronic pain, while the American Pain Society (APS) promoted the position that pain should be considered a fifth vital sign. The APS and the American Academy of Pain Medicine (AAPM) published a landmark consensus statement in 1997 that stated long-term opioid analgesic use for chronic noncancer pain posed minimal risk of overdose or addiction [31; 41]. The pharmaceutical industry was also instrumental in the movement toward loosening opioid prescribing constraints and broadening the indications for opioid use in managing chronic pain [31; 42]. Professional pain societies wrote consensus statements claiming little risk of addiction or overdose in patients with pain and that long-term opioids were easy to discontinue. In 1997, Congress passed SB402, also known as The Pain Patient's Bill of Rights [43]. In 2001, the Joint Commission issued new standards requiring hospi-

RETAIL PURCHASES[a] OF PRESCRIPTION OPIOIDS (GRAMS OF DRUG)—UNITED STATES, 2010–2019			
Opioid	**2010**	**2019**	**Change**
Methadone	15,466,040 g	15,080,444 g	-2.49%
Oxycodone	63,691,987 g	35,929,260 g	-43.59%
Fentanyl base	528,969 g	193,531 g	-63.41%
Hydromorphone	1,407,927 g	987,221 g	-29.88%
Hydrocodone	39,096,895 g	20,040,962 g	-48.74%
Morphine	22,915,640 g	11,966,623 g	-47.78%
Codeine	16,141,776 g	12,105,985 g	-25%
Meperidine	2,333,167 g	292,694 g	-87.46%
Total	161,582,401 g	96,596,720 g	-40.22%
[a]Purchasers include pharmacies, hospitals, practitioners, teaching institutions, and treatment programs.			
Source: [51; 52]			*Table 5*

tals to make pain assessment routine and pain treatment a priority. The now familiar pain scale was introduced, with patients asked to rate their pain from 1 to 10 and circle a smiling or frowning face, and pain became the fifth vital sign [44]. Immediately following the release of the new standards, concern was raised that the standards would lead to the inappropriate use of opioids. By 2002, pain as a "fifth vital sign" in the standards was changed to "pain used to be considered the fifth vital sign," and by 2004, this phrase no longer appeared in the Joint Commission's Accreditation Standards manual [45]. The standard that pain be assessed in all patients also remained controversial for two reasons: It seemed inappropriate for some patients due to the nature of their medical condition; and no similar standard existed requiring the universal assessment of other symptoms [45]. Thus, in early 2016, the Joint Commission began revising its pain assessment and management standards, with a focus on acute pain in the hospital setting. Draft standards were published in 2017 and implemented in 2018 [46; 47].

The financial support supplied to professional societies by drug companies helped influence members to change prescribing practices. Patient advocacy groups, often guided by physicians who felt constrained by the prohibition of opioid prescribing and pain specialist organization consensus that chronic pain had been previously undertreated, worked to elevate awareness that pain was untreated and unrecognized [29; 41]. During this time, opioid prescribing for chronic noncancer pain dramatically increased across the country. The movement for more aggressive pain treatment culminated in 2000, when Congress proclaimed 2000–2010 as the Decade of Pain Control and Research [48]. Shifting demographics also contributed to the changing attitudes toward opioid prescribing. With painful chronic illness rates increasing with the overall population age, there came growing awareness of the importance in providing effective pain relief [44].

Pharmaceutical companies began introducing new opioid formulations, and existing opioid products became more widely prescribed (***Table 5***). The theme of minimal abuse liability was widely used in the marketing materials distributed to prescribers and pharmacists [49]. When the escalating rates of addiction, diversion, and fatal overdose involving prescribed opioids became apparent, the same pain specialists and organizations, pain advocacy groups, drug companies, and media reinforced the perception of opioid legitimacy by primarily attributing the growing individual and public health hazard to improper Internet availability, illicit diversion, and the prevalence of societal drug addiction tendencies [50].

OXYCONTIN SALES AND PRESCRIBING, 1996–2002				
Year	**Sales**	**Increase from Previous Year**	**Number of Prescriptions**	**Increase from Previous Year**
1996	$44,790,000	N/A	316,786	N/A
1997	$125,464,000	180%	924,375	192%
1998	$286,486,000	128%	1,910,944	107%
1999	$555,239,000	94%	3,504,827	83%
2000	$981,643,000	77%	5,932,981	69%
2001	$1,354,717,000	13%	7,183,327	21%
2002	$1,536,816,000	13%	7,234,204	7%

Source: [44] *Table 6*

THE OXYCONTIN STORY: A CASE STUDY

The story of extended-release oxycodone, marketed as OxyContin, is informative and unique. Although the United States has experienced several waves of widespread prescription drug abuse over the past 150 years, the rapid ascent of OxyContin from market entry to miracle drug for chronic pain to a demonized substance of abuse and diversion on a vast scale is without precedent. Multiple factors facilitated this phenomenon. OxyContin contains a larger amount of high-potency opioid than short-acting opioid formulations. The delayed-release mechanism was easy to circumvent by chewing and swallowing or by crushing the pill and then injecting or snorting the powder. This produced a rapid, powerful opioid effect on par with heroin. Large profits were also possible from illicit sales of OxyContin, which generally commanded a black market value of $1 per milligram (with higher prices in more rural areas) [53]. In addition, the original product labeling warned against crushing the tablets because rapid release of a potentially toxic amount of oxycodone would ensue, alerting abusers on how to best achieve maximum drug effect. The original labeling also included the FDA-condoned statement that the extended-release (ER) mechanism of OxyContin presented a lower abuse potential than other oxycodone products. Perhaps most importantly, its release coincided with the growing acceptance of opioids in pain treatment and the aggressive sale and marketing tactics of its producer, Purdue Pharma [44].

The timing of product launch was fortuitous. Until the 1990s, Schedule II opioids were primarily limited to use in operating rooms and inpatient settings because they required intravenous or intramuscular administration. This posed a serious obstacle to patients with chronic pain who required high-potency opioids. In response to the increasingly permissive climate and by genuine unmet patient need, several high-dose ER formulations of pre-existing opioids were introduced to market. MS Contin, an ER version of morphine sulfate, was introduced in 1985 but was primarily limited to use in cancer pain, partially a result of the stigma surrounding morphine. OxyContin was introduced in late 1995, at the point in time when prescriber attitudes were shifting from fearing iatrogenic addiction to developing a sense of security with prescribing opioid analgesics [44].

To help ensure product success, innovative approaches were employed to elevate visibility and encourage OxyContin prescribing, as well as highly aggressive marketing and sales tactics. The amount of money spent in promotion, marketing, and sales was unprecedented for an opioid, exceeding $200 million in 2001 alone [54]. Marketing and

promotion efforts and the timing of the product launch resulted in a tenfold increase in OxyContin prescribing and sales revenue in just three years' time (***Table 6***).

In addition to the usual doctor-directed ads in medical journals, a novel indirect marketing campaign involving "nonbranded education" was implemented. Direct-to-consumer advertising of opioid drugs was prohibited, so the concept of pain relief from opioids was promoted to consumers without explicit mention of OxyContin. The public-education program Partners Against Pain (PAP) was launched, with videos, patient pain journals, and an elaborate website that marketed (to prescribers and patients) the message that pain was widespread and treatable with opioid analgesics [55]. The FDA later stated that the PAP website did provide information about OxyContin specifically and also contained a "Find a Doctor" feature to link consumers to physicians in their geographic area known to be willing to prescribe OxyContin [44].

More than 40 national pain-management and speaker-training conferences were conducted between 1996 and 2001. Thousands of prescribers attended the all-expenses-paid symposia held in resort locations [54]. From 1996 to July 2002, more than 20,000 pain-related educational programs and continuing medical education offerings for prescribers were funded by pharmaceutical sponsorship or financial contribution. This included a program that educated hospital physicians and staff on hospital and postoperative pain treatment compliance with Joint Commission pain standards. Pharmaceutical funding was used to underwrite the cost of the Joint Commission pain management educational programs, including the distribution of educational videos and a book on pain management (sold on the Joint Commission's website) [54]. Pharmaceutical funding has also paid for websites that provided free continuing medical educational on pain management; numerous pain management websites; groups such as the American Chronic Pain Association, the AAPM, and the APS; and a youth-focused website [44].

In 1999, pharmaceutical sales representatives were reportedly given 14,000 copies of a promotional video for physician distribution. Physicians were instructed to encourage patient viewing in their waiting rooms or as a "check-out" item and to use the video as an educational tool for office or hospital staff. The FDA later stated they were not provided the video before distribution for detection of inaccurate or unfounded claims, of which they later found several examples [44]. A patient starter coupon program was initiated that provided patients with a free limited-time prescription. Roughly 34,000 coupons had been redeemed when the program ended in 2001 [44; 54].

Between 1996 and 2000, the internal sales force of the pharmaceutical firm that produces OxyContin grew from 318 representatives to 671, and a bonus system was implemented to encourage OxyContin sales [54]. The company is said to have maintained an active database containing nationwide profiles of individual physicians and their prescribing patterns, allowing for the identification of high-end and low-end OxyContin prescribers by zip code, county, and state; practices with large numbers of patients with chronic pain; and high prescribers of the company's older product MS Contin [54]. Sales representatives were reportedly directed to high opioid prescribers in their sales territories, with the goal of expanding the primary care OxyContin prescribing base. Sales representatives were also directed to call on oncology nurses, consultant pharmacists, hospices, hospitals, and nursing homes [44].

In 1996, the majority of ER opioid prescriptions went to cancer patients, but by 2000, only 3% of OxyContin prescriptions came from oncologists [56; 57]. Opioid medications, and OxyContin in particular, had been successfully promoted as the first-line therapy for an increasingly wide range of moderate-to-severe pain conditions. Family practice physicians became the largest group of OxyContin prescribers, accounting for 21% of prescriptions in 2000 and close to 50% in 2003 [54; 55]. This was followed by the growing concern that, in a managed care system, time constraints imposed on primary care physicians did not allow sufficient time to evaluate and follow patients with complex chronic pain [54].

The most critical issue and source of greatest prescriber concern was the risk of iatrogenic addiction. To help counter this perception, promotion and marketing to healthcare professionals and patients alike emphasized that OxyContin prescribing carried little risk of addiction. Misrepresenting this risk proved costly. In 2007, the pharmaceutical company paid $634 million in fines following guilty pleas from three of its executives to criminal charges for promoting false claims that OxyContin was less addictive and less subject to abuse and diversion than other opioids [54].

The escalating rates of OxyContin misuse were integral to the growing nationwide problem of prescription opioid abuse, diversion, addiction, and overdose. By 2004, OxyContin had become the most prevalent prescription opioid abused in the United States. Predictably, this public health epidemic created a backlash from regulatory and law enforcement agencies [58].

THE PAIN MANAGEMENT MOVEMENT

By the mid-2000s, professional and law enforcement efforts had emerged to curtail OxyContin abuse, including the pain management movement and creation of the pain management subspecialty. However, these efforts had some unintended negative consequences. Pharmacists were tasked with evaluating legal prescription appropriateness through a "drug use review." Encouraged by drug enforcement authorities, some became adversaries of physicians and patients by reporting any out-of-the-ordinary prescribing to the police [58].

Legitimate OxyContin use was also tarnished by negative media coverage suggesting that drug diversion was the result of irresponsible prescribing practices. A 2011 study of OxyContin coverage content in lay media and professional publications found that abuse, addiction, crime, and death were emphasized, typically from law enforcement and the criminal justice system perspectives. The majority of patients with legitimate medical need who benefited from the drug were rarely mentioned. An unfortunate outcome is the stigma sometimes experienced by patients who require OxyContin for long-term pain control [59].

EPIDEMIOLOGY OF CHRONIC PAIN AND OPIOID USE

Chronic pain costs the nation up to $635 billion each year in medical treatment and lost productivity. It also affects about 100 million American adults—more than the total affected by heart disease, cancer, and diabetes combined [7]. The lifetime prevalence of chronic pain ranges from 54% to 80%, and among adults 21 years of age and older, 14% report pain lasting 3 to 12 months and 42% report pain persisting longer than 1 year [7]. An estimated 41% of patients with chronic pain report their pain is uncontrolled, and 10% of all adults with pain suffer from severe, disabling chronic pain.

The increasing prevalence of chronic pain is the result of multiple factors, including the aging population; rising rates of obesity and obesity-related pain conditions, such as joint deterioration; advances in lifesaving trauma interventions; poorly managed post-surgical pain; and greater public awareness of pain as a condition warranting medical attention [7]. In addition, many armed forces veterans have been returning from military action in Afghanistan and Iraq with traumatic injuries and chronic pain, and veterans' care clinicians have been reporting the perception that long-term pain management is lacking support in the veteran healthcare infrastructure [60].

The extent of opioid analgesic use in the United States today is unprecedented in the country's history and unparalleled anywhere in the world. Before 1990, prescribers in the United States were skeptical of prescribing opioids for chronic noncancer pain. But as of 2017, nearly 58 opioid prescriptions were written for every 100 Americans, and more than 17% of Americans had at least one opioid prescription filled, with an average of 3.4 opioid prescriptions dispensed per patient [52]. Sales of opioid analgesics now total an estimated $25.4 billion each year [61].

Worldwide consumption of opioid analgesics has increased dramatically in the past few decades, with the United States driving a substantial proportion of this increase. For example, the 1990 global consumption of hydrocodone was 4 tons (3,628 kg), compared with the 2018 consumption of 25.8 tons (23,486 kg); 25.6 tons of this were consumed in the United States. Similarly, 3 tons (2,722 kg) of oxycodone were consumed globally in 1990, versus 65.9 tons (59,856 kg) in 2018, of which 48.8 tons (37,946 kg or 63%) were consumed in the United States [62]. With only 4.25% of the world's population, the United States annually consumes more than 84% of all opioid supplies, including [62]:

- 99% of all hydrocodone
- 63% of all oxycodone
- 40% of all methadone
- 45% of all hydromorphone
- 24% of all meperidine
- 22% of all fentanyl

This disproportionate rate of opioid consumption reflects sociocultural and economic factors and standards of clinical medicine.

Between 1992 and 2003, the U.S. population increased 14%, while persons abusing opioid analgesics increased 94% and first-time nonmedical opioid analgesic users 12 to 17 years of age increased 542% [48]. To assist in monitoring the public health problem associated with prescribed opioids, numerous governmental, nonprofit, and private sector agencies and organizations are involved in collecting, reporting, and analyzing data on the abuse, addiction, fatal overdose, and treatment admissions related to opioid analgesics (***Table 7***) [63].

In 2018, an estimated 15.5 million prescriptions (9% of 169 million opioid analgesic prescriptions) were dispensed for ER/LA opioid analgesics from U.S. retail pharmacies. Five million prescriptions (33%) were for ER morphine; 3 million (20%) were for fentanyl transdermal patch; 3 million (19%) were for single-ingredient ER oxycodone; and 2 million prescriptions (13%) were dispensed for methadone. Similar trends were observed from 2014 through 2017 [64]. The total number of ER oxycodone (e.g., OxyContin and others) prescriptions declined from 4.6 million in 2014 to 3.0 million in 2018 and the total number of ER oxymorphone prescriptions declined from 1 million in 2014 to approximately 353,000 in 2018 [64]. The total number of prescriptions for ER morphine (e.g., Kadian, MS Contin, Avinza) decreased from 6.3 million in 2014 to 5 million in 2018 [64]. ER hydromorphone (e.g., Exalgo), introduced in 2010, was prescribed an estimated 186,000 times in 2014 and 100,000 times in 2018 [64].

AGENCIES INVOLVED IN COLLECTING AND REPORTING DATA ON NONMEDICAL OPIOID ANALGESIC USE	
Agency [Sponsor]	**Activities**
National Institute on Drug Abuse [NIH, DHHS]	Conducts research involving drug abuse and addiction, tracks trends, disseminates results to improve drug abuse and addiction prevention, treatment, and policy
Monitoring the Future Survey [NIDA, ISR]	Collects data related to drug, alcohol, and cigarette use and attitudes in public and private secondary school students in 8th, 10th, and 12th grade
Drug Abuse Warning Network [SAMHSA]	Monitors drug-related hospital emergency visits and deaths to track the impact of drug use, misuse, and abuse; conducts retrospective review of medical records and case files
Drug Evaluation Network System [TRI, ONDCP]	Generates reports to assist in treatment planning, tracks changes in patient function over time, tracks trends in drug usage, monitors program performance and prepares mandated reports to government and elected officials, maintains an electronic data collection system
The National Epidemiologic Survey on Alcohol and Related Conditions [DHHS/NIH/NIAAA]	Provides information on alcohol use and nonmedical use of prescription opioids (excluding methadone and heroin), sedatives, tranquilizers, and amphetamines in non-institutionalized populations 18 years of age and older
The National Survey on Drug Use and Health [SAMHSA's OAS, DHHS, RTI]	Obtains statistical information related to illicit drug use, administers population-level questionnaires to non-institutionalized residents 12 years of age and older through in-person interviews to obtain data on illicit and prescription drug use
The National Center on Addiction and Substance Abuse at Columbia University [private funding]	Studies and combats substance abuse, surveys children, teens, college students, parents, other adults, prisoners, and women receiving temporary assistance
Researched Abuse, Diversion, and Addiction-Related System [Purdue Pharma, Rocky Mountain Poison Control Center]	Collects product- and locality-specific data; measures rates of abuse, misuse, and diversion to help understand trends; helps develop interventions; assists pharmaceutical companies in regulatory adherence; operates a prescription drug abuse, misuse, and diversion surveillance system
The Arrestee Drug Abuse Monitoring Program [NIJ]	Collects data related to newly booked arrestees regarding drug use, drug and alcohol dependence, treatment, and drug market participation
The National Poison Data System [AAPCC]	Provides a real-time comprehensive poisoning surveillance and toxicovigilance database, operates a uniform data set from the AAPCC
Office of the Medical Investigator (OMI) [city, county, and state governments]	Investigates deaths that come under the jurisdiction of the OMI, including poisoning and drug-related fatalities
AAPCC = American Association of Poison Control Centers, DHHS = U.S. Department of Health and Human Services, ISR = Institute for Social Research, NIAAA = National Institute on Alcohol Abuse and Alcoholism, NIDA = National Institute on Drug Abuse, NIH = National Institutes of Health, NIJ = National Institute on Justice, ONDCP = White House Office of National Drug Control Policy, RTI = Research Triangle Institute, SAMHSA's OAS = Substance Abuse and Mental Health Services Administration, TRI = Treatment Research Institute.	
Source: [63]	*Table 7*

An estimated 44 million total oxycodone prescriptions were dispensed in 2018. Oxycodone-containing IR products accounted for 56% (25 million prescriptions), followed by single-ingredient oxycodone IR at 37% (16 million prescriptions) and single-ingredient oxycodone ER at 7% (3 million prescriptions) [64]. From 2015 to 2018, the number of prescriptions dispensed for combination oxycodone-containing IR products decreased by 27%, from 34 million in 2015 to 25 million in 2018 [64]. The total number of prescriptions dispensed for single-ingredient oxycodone IR remained stable from 2014 to 2018, whereas the number of prescriptions dispensed for single-ingredient oxycodone ER decreased by 36%, from 5 million in 2014 to 3 million in 2018 [64].

In 2018, primary care practitioners (e.g., general practice, family practice, internal medicine) accounted for approximately 41% of total prescriptions dispensed for single-ingredient oxycodone ER from retail pharmacies in the United States. Anesthesiologists and physical medicine and rehabilitation specialists accounted for 19% and 11%, respectively [64].

In 2018, the Drug Enforcement Agency's Automation of Reports and Consolidated Orders System (ARCOS) reported that the number of dosage units distributed nationwide at the retail level (i.e., hospitals, pharmacies, practitioners, treatment programs, and teaching institutions) was down from 2017. However, opioids continued to rank as fifth out of the seventh most distributed controlled prescription drugs. Hydrocodone and oxycodone products were dispensed at more than twice the rate of any other controlled prescription drug [65]. Although the amount of prescription opioids available on the legitimate market has declined each year since peaking in 2011, the number of prescription opioids available in 2018 remained significant. ARCOS indicated that 10.8 billion dosage units of opioid controlled prescription drugs were manufactured and distributed in 2018. Of that number, more than 79% were oxycodone and hydrocodone products [65].

Prescribing rates are down overall, but they vary widely between states, particularly at the county level. The nationwide prescribing rate for 2017 was 58.5 prescriptions per 100 persons, yet some counties had rates that were seven times higher than the national average. For example, Alabama and Arkansas had the highest prescription rates (greater than 100 prescriptions for 100 people), while New York and Hawaii had the lowest rates at 37.8 and 37 prescriptions per 100 people, respectively [65].

FACTORS THAT INFLUENCE OPIOID ANALGESIC PRESCRIBING

A decision to prescribe opioids is based on clinician knowledge and judgment and also on patient preference, availability of non-opioid pain treatment approaches, the complexities and bias in third-party reimbursement, aggressive pharmaceutical marketing, and medico-legal concerns. These and other factors have tended to skew the standard of care toward reliance on opioids for long-term chronic pain management in the past few decades [8].

The use of patient satisfaction as a barometer of clinician skill may also influence opioid analgesic prescribing. Satisfaction with clinical care can be obtained from patient surveys, commonly including questions about how adequately their pain was addressed by the provider. Numerous for-profit provider-grading websites offer patients a forum to broadcast their opinions of care received from physicians. Healthcare professionals are likely to get a poor rating from patients who were refused opioids over abuse concerns, and reimbursement and job security can be adversely impacted by negative patient survey ratings in some institutions [66].

The financial structure of many managed care firms and third-party carriers incentivizes pain treatment and discourages substance abuse or addiction treatment. From a financial reimbursement perspective, the time spent providing patient education and counseling related to addiction issues has become one of health care's least valued commodities. This is especially the case in emergency department (ED) settings, where evaluation is often based on patient volume and not on time spent with individual patients. As such, it is faster and pays better to diagnose pain and prescribe an opioid than to diagnose and treat addiction [66].

Increasing Population Rates of Chronic Pain

Any discussion of the rising rates of opioid analgesic prescribing should also acknowledge the increasing prevalence of chronic pain in the United States, with data showing increasing rates over the past several decades that are projected to continue in the future. Musculoskeletal conditions are the most common type of chronic pain, with back pain the most common type of chronic musculoskeletal pain [67]. Increases in low back pain prevalence and associated disability have been quantified in several studies. For example, an investigation of low back pain rates over a 40-year period found increases in prevalence from 8.1% in 1956–1958 to 17.8% in 1994–1995 in men, and 9.1% to 18.2% in women [68]. A comparison of back pain prevalence in North Carolina between 1992 and 2006 found an increase in chronic, impairing low back pain, from 3.9% in 1992 to 10.2% in 2006, and an 11.6% annual increase in healthcare utilization and disability [69]. Data from the National Center for Health Statistics estimate that in 2016 20.4% (50.0 million) of adults in the United States had chronic pain and 8.0% (19.6 million) had high-impact chronic pain (defined as pain that limits life or work activities on most days or every day in the past six months), with higher prevalences of both types of pain reported among women, older adults, previously but not currently employed adults, adults living in poverty, adults with public health insurance, and rural residents [70].

OPIOID ANALGESIC-RELATED MORBIDITY

There are a number of ways that the larger picture of opioid analgesic-related morbidity may be examined. Because the effects of opioid analgesic misuse can manifest in many ways in a variety of settings, it is important to examine data from different sources in order to get an accurate picture of opioid-related morbidity in the United States.

Emergency Department Admissions

The Drug Abuse Warning Network (DAWN) was established in 1972 by the Drug Enforcement Administration to track and publish data collected from participating states on ED visits resulting from substance misuse or abuse, adverse reactions, drug-related suicide attempts, and substance abuse treatment [71]. By its final year in 2011, legacy DAWN had collected data from metropolitan areas in 37 states, with complete coverage in 13 states. Although their total figures did not capture all 50 states, the population rates were representative and able to be extrapolated to the United States as a whole [72].

In 2011, the overall admission rate for misuse or abuse of opioid analgesics (excluding adverse reactions) was 134.8 per 100,000, an increase of 153% compared with 2004. In the 13 states involved in the legacy DAWN network, the top four opioid analgesics involved in drug-related ED visits for 2011 were various formulations of oxycodone (175,229), hydrocodone (97,183), methadone (75,693), and morphine (38,416). Between 2004 and 2011, ED admissions increased 74% for methadone, 220% for oxycodone, 96% for hydrocodone, and 144% for morphine. Importantly, there was no meaningful change in ED admission rates involving opioid analgesics between 2009 and 2011. If this is also borne out by subsequent data, it strongly suggests a plateau in the misuse and abuse rates of these agents [72].

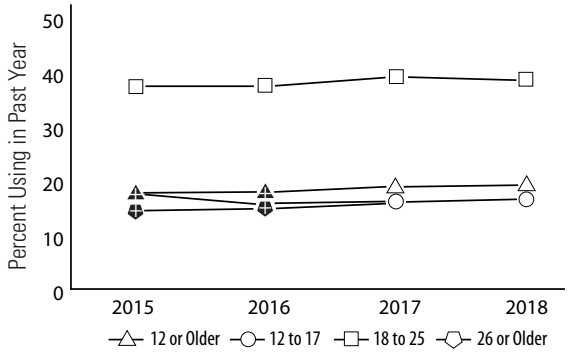
As of 2020, the Substance Abuse and Mental Health Services Administration (SAMHSA) is re-establishing DAWN and will retain the important aspects of legacy DAWN. In comparison to legacy DAWN, the re-established DAWN will function as a smaller-scale sentinel surveillance system, or an early-warning system. The new DAWN will focus on detecting "outbreaks" (i.e., sudden increases in ED visits for specific drugs), identifying new and novel psychoactive substances, monitoring the magnitude of the health effects from substance use (as reflected in ED visits), and documenting the geographic, temporal, and demographic distribution of the problems to inform planning and policy at the local, state, and national levels [73].

Nonmedical Use of Prescription Opioids

In 2018, 10.3 million people reported nonmedical use of opioid analgesics (i.e., use without a prescription or for the non-analgesic effect) and 3.8 million were first-time nonmedical users that year [74]. An estimated 3.4 million people misused oxycodone products (including OxyContin) in the past year (1.2% of the population) [74]. The most frequent initial (past year) drug used was cannabis (43.5 million), followed by nonmedical use of prescription opioids (9.9 million), nonmedical use of tranquilizers (6.4 million), hallucinogens (5.6 million), cocaine (5.5 million), stimulants (5.1 million), inhalants (2.0 million), methamphetamine (1.9 million), and heroin (808,000) [74].

Among youths 12 to 17 years of age, those reporting past-year nonmedical opioid analgesic use remained fairly stable between 2015 and 2018 (***Figure 1***), whereas, according to NSDUH data for adults 18 to 25 years of age, the percentage reporting past-year nonmedical opioid analgesic use increased from 4.2% in 2015 to 5.6 in 2018 [74].

PAST-YEAR NONMEDICAL OPIOID ANALGESIC USE AMONG PEOPLE 12 YEARS OF AGE OR OLDER: 2015–2018



Source: [74] *Figure 1*

Rates of Prescription Opioid Abuse and Addiction

In 2018, 2.0 million persons had opioid analgesic abuse or dependence, similar to the number in 2012 (2.1 million). The percentage of people 12 years of age or older in 2018 with an opioid use disorder was similar to the percentages in 2016 and 2017, but it was lower than the percentage in 2015 [74].

Widespread opioid analgesic prescribing and nonmedical use, abuse, and dependence are not unique to the United States. Canadian estimates for 2009 indicated that of the total population, 19.2% used prescription opioid analgesics, including nonmedical use by 4.8%, and that 0.4% used the drugs nonmedically to get high. The past-year nonmedical use prevalence of 1 in 20 adults was comparable to U.S. rates. Although the study found high rates of prescribed opioid analgesic use and nonmedical use, most noteworthy was the conclusion that opioid analgesic prescribed use, nonmedical use, and nonmedical use to get high was not associated with the level of prescription opioid dispensing. This finding stands in contrast to the stream of reports over the past decade from the CDC, the DEA, and other governmental agencies in the United States [75].

SAMHSA data do differentiate the underlying basis of misuse. For instance, a person who took or received a prescription opioid from a relative or friend for a headache is recorded as a nonmedical user (abuser); although placed in the same category as someone who stole prescription opioids from a medicine cabinet to get high, the motivations and possible interventions for the respective problems are entirely different. The importance of this distinction is clear in a large 2008 survey of high school seniors, which found that 12.3% had used opioid analgesics for nonmedical reasons at some point [76]. This is similar to a 2012 study of 7,374 high school seniors, which found that 12.9% reported lifetime nonmedical use of prescription opioids [77]. A multi-cohort national study of more than 8,000 high school seniors found that 36.9% of past-year nonmedical users of prescription opioids obtained the medications from their own previous prescriptions. Analyses indicated that these users were primarily motivated by a desire to relieve physical pain [78]. This should lead to exploration of important public health questions, such as why so many young persons suffering from untreated (or mistreated) physical pain resort to self-medication [77; 78].

Opioid Use Disorders in Patients with Pain Receiving Long-Term Opioid Analgesics

The literature examining opioid use disorder incidence in patients with chronic pain receiving opioid analgesic therapy have reported rates of addiction developing during opioid therapy ranging from 0.03% to 50% [79; 80]. These vast differences are mainly the result of widely varying criteria to define opioid addiction. Many of the studies used diagnostic criteria according to the DSM-IV, or the DSM-III in studies that began before 1994. The DSM-III and IV criteria include tolerance and withdrawal as diagnostic criteria, which can reflect physical dependence that is an expected development of long-term opioid therapy. Other DSM diagnostic criteria may also describe common non-addiction based experiences of patients with pain who are receiving long-term opioid therapy, such as using the medication in higher amounts or for a longer term than intended and a persistent desire or unsuccessful attempts to cut down, control, or halt the use of the opioids [81]. Also, DSM criteria require the patient experience of impaired function or distress resulting from their opioid use. Many of those with chronic pain report clinically significant dysfunction and distress from their chronic pain; some studies do not clarify whether pain or the opioid is causing the reported dysfunction and distress. For these reasons, more recent pain researchers have concluded that DSM criteria are not applicable and may be misleading as a diagnostic basis in patients with chronic pain [79; 82].

One study that controlled for the improper fit of DSM opioid addiction criteria in patients receiving long-term opioid therapy followed a group of patients with sickle cell anemia [83]. Researchers found that 31% of patients receiving opioids developed opioid dependence according to the DSM-IV criteria. When pain-related symptoms that actually accounted for positive diagnostic criteria were removed, the addiction incidence fell to 2% [83]. In a review of 24 studies enrolling 2,507 patients with chronic pain with a 26.2-month average duration of opioid therapy, the overall opioid addiction rate was 3.27% [80]. A 2013 study evaluated the rate of drug misuse and illicit use in 1,350 patients with a pain duration greater than one year who were currently prescribed opioids for three months or longer and enrolled in an interventional pain program. The study found that 1.3% were using non-prescribed prescription drugs and 7.9% were using illicit drugs (primarily cannabis; substantially fewer for cocaine and methamphetamine). The authors concluded the rates they found in patients receiving opioids were comparable to those of the general population [84].

Treatment Admissions for Opioid Use Disorders

Among persons 12 years of age or older, treatment admissions for prescribed opioid abuse have more than doubled in the last decade. Those whose most recent past-year treatment was for prescription opioids numbered 360,000 persons in 2002; this increased to 3.8 million in 2018 [74].

Diversion of Prescription Opioids

Research has more closely defined the location of prescribed opioid diversion into illicit use in the supply chain from the manufacturer to the distributor, retailer, and the end user. This information carries with it substantial public policy and regulatory implications. The 2018 NSDUH data asked nonmedical users of prescription opioids how they obtained their most recently used drugs [74]. Among persons 12 years of age or older, 51.3% obtained their prescription opioids from a friend or relative for free, 34.7% got them through a prescription from one doctor (vs.18.1% in 2010–2011), 9.5% bought them from a friend or relative, and 6.5% bought them from a drug dealer or other stranger. Less frequent sources included stealing from a friend or relative (3.2%); multiple doctors (2.0%); theft from a doctor's office, clinic, hospital, or pharmacy (0.9%) (vs. 0.2% in 2009–2010); and some other way (4.6%) [74].

Neonatal Abstinence Syndrome (NAS)

Rates of opioid misuse may also be tracked by unintended effects of use during pregnancy on newborns. Cases of neonatal abstinence syndrome (NAS)—a group of problems that can occur in newborns exposed to prescription opioids or other drugs while in the womb—grew by 433% in the United States between 2004 and 2014 [85].

OPIOID ANALGESIC-RELATED MORTALITY

Opioid analgesics may result in deaths due to unintentional or intentional overdose or intoxication-related accidents. However, the majority of data focus on unintentional overdose. The rates of fatal toxicity involving prescription opioid analgesics have escalated in tandem with the increasing rates in opioid analgesic prescribing, abuse, addiction, and diversion. Unfortunately, additional valuable information is not revealed by the mortality data, such as whether the potential cause of the fatality was opioid ingestion for intoxication or for pain control, or whether the decedent was taking the medication as prescribed, using the opioid nonmedically (e.g., for insomnia control), using the medication plus someone else's prescribed opioid for poorly managed pain, or taking someone else's prescribed opioid to get high. Also unknown is the relative contribution of the opioid to the fatality. In one postmortem study of fatalities involving prescription opioids, 79% of decedents also tested positive for alcohol and other drugs [86]. In the absence of more details surrounding opioid fatalities, crafting preventive measures is difficult, and estimates of the true fatality rate from prescription opioids remain elusive.

Regional differences have been found in fatal drug overdose involving opioids, with the highest rates occurring in the Southwest and Appalachian regions. Differences between states have also been found. Data from 2018 indicate the highest fatal drug overdose rates occurred in West Virginia (51.5 per 100,000), Delaware (43.8 per 100,000), Maryland (37.2 per 100,000), Pennsylvania (36.1 per 100,000), Ohio (35.9 per 100,000), and New Hampshire (35.8 per 100,000. Drug overdose deaths decreased by 4.6% from 2017 to 2018 [87]. Significant increases in drug overdose death rates during this period were primarily seen in California, Delaware, Missouri, New Jersey, and South Carolina [87].

According to one analysis, nearly one in four people on Medicaid received prescription opioids in 2015 [88]. The report analyzed 1.8 million opioid prescriptions written for 3.1 million Medicaid members across 14 states. According to the CDC, Medicaid patients are prescribed opioids at twice the rate of non-Medicaid patients and are at six times the risk of overdose [89]. However, essential information was omitted in this CDC report but uncovered by an investigation into Washington state opioid fatalities [90]. Left out of the CDC publication was the policy decision in early 2004 by the State of Washington to list methadone as a preferred opioid analgesic, as a cost-cutting measure. Morphine was the only other long-acting opioid placed on the preferred analgesics list. Methadone fatalities increased from 140 in 2002 to 256 in 2004. Many of these fatalities involved the combination of methadone and other prescribed medication, particularly benzodiazepines and antidepressants; of the 274 methadone-related fatalities in 2009, prescribed medications for anxiety or other mental-health concerns were found in 43% of decedents. The number of methadone fatalities in 2006 was 300% greater than the number attributed to any other long-acting pain reliever. Although the escalation in methadone fatalities had become obvious, the cost-cutting objectives were significant and state officials maintained the stance that methadone was safe and effective [91].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Interventional Pain Physicians recommends methadone for use after failure of other opioid therapy and only by clinicians with specific training in its risks and uses.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed August 21, 2020.)

Level of Evidence: I (Evidence obtained from multiple relevant high quality randomized controlled trials for effectiveness)

Gender Differences

The opioid overdose rate among women has increased faster than it has in men. From 1999 to 2010, overdose fatality increased by more than 400% in women, compared to 265% for men; during this period, nearly 48,000 women died of opioid analgesic overdose. In aggregate, women tend to possess background characteristics and opioid analgesic use patterns that may contribute to overdose vulnerability. Women are more likely to experience chronic pain, receive prescriptions for opioid analgesics, receive higher doses of opioids, and use opioids for longer periods than men. Substance use disorders involving opioid analgesics are thought to develop more rapidly in women, and women may be more likely to obtain opioid prescriptions from multiple prescribers than men [92].

Women 25 to 54 years of age have the highest rate of ED admission for opioid misuse or abuse, and the greatest risk of prescription opioid fatality occurs in women 45 to 54 years of age. Non-Hispanic white and American Indian or Alaska Native women have the highest mortality risk from prescription opioids, and opioid analgesics are involved in 1 in 10 suicides among women [92].

Overdose Fatality and Prescribed Opioid Dosage

Several studies have reported a positive association between high-dose opioid prescribing and overdose risk. However, these studies utilized methods in design and data analysis that cast doubt on the results, such as failure to control for the possible effect of opioid abuse on overdose outcomes and differences in the indications, formulations, and opioid products in patients prescribed high versus low dosing [93].

A study was conducted to re-examine the relationship between opioid dose and overdose risk while controlling or eliminating the methodological shortcomings in previous studies. The records of 38,861 patients prescribed morphine ER, transdermal (patch) fentanyl, or buprenorphine patch between 2005 and 2010 were evaluated. High-dose was defined as 120 mg morphine equivalent dose (MED) or more; low-dose included 30 mg MED or less. The rates of overdose were 0.7% with morphine ER, 0.4% with fentanyl patch, and 0.3% with buprenorphine patch. The relative risk of overdose among patients prescribed high doses was 1.44 for morphine ER, 1.51 for fentanyl patch, 0.78 for buprenorphine patch, and 1.18 when all three opioids were combined. These results indicate a roughly 1.5 times greater overdose risk with high-dose morphine and fentanyl than with low-dose, no difference in overdose risk between high- and low-dose buprenorphine, and an overall overdose risk markedly lower than previous reports [93].

This data should be considered tentative as it was presented at a conference and, as of 2020, has not yet been published in a peer-reviewed journal. As with the previous research, this study was performed retrospectively and not prospectively, which can lessen the validity of the results. However, in light of these limitations, the results provide a credible counterbalance to previously published figures.

Contributory and Risk Factors for Overdose

The reasons for opioid analgesic overdose fatalities are multifactorial and include prescriber behaviors, patient contributory factors, nonmedical use patterns, and systemic failures. Risk factors identified for fatal opioid toxicity include [6]:

- Prescriber error due to knowledge deficits
- Patient nonadherence to medication regimen
- Unanticipated medical and mental health comorbidities, including substance use disorders
- Co-administration of other CNS-depressant drugs, including alcohol, benzodiazepines, and antidepressants
- Sleep-disordered breathing (e.g., sleep apnea)
- Body mass index of 30 or greater

Additional factors specifically contributing to methadone fatality include [94]:

- Payer policies that encourage or mandate methadone as first-line therapy
- Methadone prescribing in opioid-naïve patients
- Lack of prescriber knowledge of methadone pharmacology

A population-based study examined patterns and characteristics of opioid users in Ontario, Canada, whose cause of death involved opioid toxicity [95]. Between 2006 and 2008, 2,330 drug-related deaths were identified, of which 58% were partially or entirely attributed to opioids. The manner of death was classified by a coroner as accidental (68%), undetermined (16.3%), or suicide (15.7%). Among decedents, at least 7% ingested opioids that were prescribed to friends or a family member; 19% altered the route of administration through injection, inhalation, or chewing a transdermal patch; 3% had been released from incarceration just before their death; and 5% had switched from one opioid to another near the time of death [95]. Differences were found between decedents who died accidentally versus suicide. A personal history of substance abuse, enrollment in a methadone maintenance program, cirrhosis, hepatitis, and cocaine use were significantly associated with accidental death. Mental illness, previous suicide attempts, chronic pain, and a history of cancer were significantly associated with death by suicide.

Methadone

Historically, methadone was used primarily as pharmacotherapy for heroin addiction. During the 1990s, however, methadone gained increased acceptance for use as an analgesic, and methadone began to be prescribed to outpatients with moderate-to-severe noncancer pain. Prescribing rates soared over the next decade; comparison of methadone sales quantity between 1997 and 2007 shows an increase of 1293% [96; 97]. This rising use of methadone occurred simultaneously with concerns over the abuse potential of OxyContin and the search for a relatively inexpensive long-acting opioid analgesic alternative [98; 99].

By 2008, two-thirds of methadone prescriptions were for pain treatment. The unique pharmacologic properties of methadone make its use in pain management complex, with greater potential for hazard than other prescribed opioids. Prescribers familiar with using methadone as opioid addiction treatment may be unaware that suppression of opioid withdrawal symptoms lasts 24 or more hours, while the analgesic duration is 4 to 8 hours, despite a half-life exceeding 60 hours in some patients. Accidental overdose fatalities can occur when patients re-administer methadone when the analgesia wears off and pain returns, potentially elevating plasma concentrations to life-threatening levels. These same pharmacological properties also imperil those who use it illicitly. Opioid abusers often co-administer benzodiazepines, which greatly elevates lethality risk with methadone. Concurrent use of alcohol poses the same risk [98; 99].

Since the mid-2000s, methadone has become disproportionately represented in cases of opioid analgesic fatality. Based on data showing that 70% of fatalities among those prescribed methadone occurred in the first seven days of treatment, the FDA changed the methadone labeling in 2006 to lengthen dosing intervals from every 3 to 4 hours to every 8 to 12 hours; the initial recommended dose of 2.5–10 mg was unchanged [6; 100]. In 2008, use of the highest oral dose preparations, 40 mg, was prohibited from use in pain treatment and restricted to addiction therapy [94].

Mortality Risk in Highly Controlled Inpatient Settings

In addition to the well-publicized risk of overdose fatality with prescribed and diverted opioid analgesics, it is worth mentioning that use of opioid analgesics carries risk even under the most tightly controlled conditions. In 2012, the Joint Commission released a *Sentinel Event Alert* entitled "Safe Use of Opioids in Hospitals," which referenced database reports of death or serious morbidity between 2004 and 2011. Of all events resulting in serious morbidity or mortality, 47% resulted from wrong medication dose errors, 29% resulted from inadequate patient monitoring, and 11% were due to other factors, including excessive dosing, medication interactions, and adverse drug reactions. Prescriber knowledge deficits in opioid pharmacology and optimum opioid route of administration (e.g., oral, parenteral, transdermal patches) accounted for some of the serious adverse patient outcomes [101]. The Joint Commission findings of serious opioid-related morbidity and mortality even when administered under highly controlled conditions and correlational data that show increased prescription opioid abuse and overdose fatality with increased opioid prescribing suggest that adverse outcomes occur at a fixed ratio to overall use [101].

Chronic Pain and Suicide by Overdose

Prolonged intense pain can destroy quality of life and the will to live, driving some patients to suicide [40]. The growing concern over opioid addiction and fatal overdose have obscured the relevant problem of intentional overdose. For many individuals, committing suicide is a way out of a situation or problem causing extreme suffering. According to DAWN, an estimated 228,366 ED visits for drug-related suicide attempts occurred in 2011 [102]. This was a 51% increase in these types of visits in individuals older than 11 years of age compared with 2005 [103]. There was a 58% increase in individuals 18 to 29 years of age, and a 104% increase in those 45 to 64 years of age [103]. Approximately 39% involved alcohol and 11% involved illicit drugs [102; 103].

Although an accurate estimate of the number of suicide attempts and completions is unknown because intent is often misclassified or not classified, risk factors for suicidal ideation are very high in the chronic pain population. Many patients with pain experience concurrent depression, and some have histories of alcohol and substance abuse. Multiple studies have shown rates of suicidal ideation and suicide attempts as high as 50% in patients suffering from chronic pain [104]. An estimated 50% of patients with chronic pain have had serious thoughts of committing suicide due to their pain disorder, and drug overdose is the most commonly reported plan for committing suicide (75%) in these patients [105; 106]. The Canadian Community Health Survey found that, after adjusting for sociodemographics and acute mental disorders and comorbidities, the presence of one or more chronic pain conditions significantly elevated the risk of suicidal ideation and suicide attempts [107]. A literature review found that risk of suicide completion was doubled in patients with chronic pain relative to non-pain controls [108].

UNTREATED/UNCONTROLLED PAIN AND MORBIDITY/MORTALITY

Mortality Risk

A link between chronic uncontrolled pain and adverse health outcomes has been identified in previous research, and the results of a 2010 study reaffirmed this association and uncovered a significant mortality risk not previously identified. Over a 10-year period, a prospective longitudinal study collected annual mortality information from a cohort of 6,940 primary care patients [109]. Survival among those reporting moderate-to-severe interference from chronic pain was significantly worse than survival among those reporting mild or no chronic pain or interference. After adjusting for sociodemographic factors and long-term disabling illness, moderate-to-severe chronic pain inflicted a 68% greater mortality risk than cardiovascular disease [109]. While considerable attention has been given to the risk of fatal toxicity and overdose involving opioid analgesics, these data suggest the mortality risk of uncontrolled, severe, chronic pain surpasses that of accidental death from toxicity or overdose with prescribed opioid analgesics.

Alterations in Brain Structure and Function

Substantial evidence indicates that poorly controlled acute pain can induce neuroplastic changes that underlie the development and perpetuation of chronic pain. Evidence from studies of uncontrolled chronic pain are now documenting changes in brain morphology, such as decreased prefrontal cortex gray matter volume in patients with chronic back pain or fibromyalgia [110]. Diminished prefrontal cortex gray matter volume is associated with adverse functional changes and decreased patient ability to engage in behaviors that can inhibit pain experience [110]. One study compared the brain morphologies of patients with chronic back pain to control subjects, and found 5% to 11% less neocortical gray matter volume among patients with back pain, an association between pain duration and volume reduction, and a loss in gray matter volume equivalent to the effects from aging 10 to 20 years [111].

ARRESTEE DATA

Researchers have found a distinctive pattern in the lifespans of drug abuse epidemics. This pattern reflects the escalating and declining prevalence in the use of a substance, the projected course into the near future, and prevalence rate variation across localities. The phases common to all drug epidemics are incubation, expansion, plateau, and decline in use of the drug. Arrestee data are a valuable source of information for tracking drug use trends and are consistent or slightly ahead of drug use data collected from general population studies in measuring drug epidemic phenomenon. To better understand the problem of prescription opioid abuse, information was obtained from 41,501 adult male arrestees in nine geographic locations. Arrestees provided data on their past three-day opioid analgesic use. Data from 2000–2003 were compared with data from 2007–2010. By location,

the prescription opioid epidemic phase and the 2010 rate of past three-day opioid analgesic use by arrestees were [112]:

- Atlanta: 4% (never became an epidemic)
- Charlotte: 8% (plateau, possibly declining)
- Chicago: 3% (never became an epidemic)
- Denver: 7% (never became widespread, now declining)
- Indianapolis: 16% (plateau)
- Manhattan: 6% (plateau)
- Minneapolis: 8% (plateau)
- Portland: 15% (plateau, possibly declining)
- Sacramento: 12% (plateau)

These results illustrate the uneven geographic distribution of the prescription opioid use epidemic. It is also clear that prevalence rates are stabilizing or declining in all localities. These arrestee data indicate the epidemic has likely peaked and predict the decline in first-time and past-year use and an increase in prescription opioid addiction and treatment-seeking rates. In susceptible persons, progression in severity of a substance use disorder to addiction often occurs over many years. Persons who now meet diagnostic criteria for opioid analgesic addiction, and may be seeking help, probably began their use during an earlier phase of the epidemic.

MITIGATING RISK IN OPIOID PRESCRIBING PRACTICE

BACKGROUND

As discussed, pain treatment, especially in the context of opioid prescribing, is defined as inappropriate by its non-treatment, inadequate treatment, overtreatment, or continued use of ineffective treatment [10]. Inappropriate pain treatment with opioid analgesics elevates the risk of uncontrolled pain, possibly serious adverse side effects, and abuse and diversion. Therefore, clinicians who treat patients with chronic pain are required to use strategies that assess and mitigate the risk of abuse liability inherent in opioids. Although risk assessment and mitigation strategies have been developed to decrease the problem of prescribed opioid abuse, diversion, and overdose, their use can also reduce the development of serious side effects and help ensure the treatment selected is benefiting the patient [113].

The 2011 Institute of Medicine report *Relieving Pain in America* reinforced the importance of framing chronic pain as a unique chronic disease state with complex neurophysiological, emotional, and social components, making its management distinct from that of acute pain [7]. Treating chronic pain differs from acute pain by the duration, multimodal approach, and risk mitigation of the therapy. Clinicians may fear that managing the issues surrounding opioid analgesic prescribing render the practice too difficult or complex [113]. To assist in the dual need of protecting one's clinical practice while reducing opioid abuse, the FSMB released a model policy for opioid analgesic prescribing in 2013. This policy was the result of identification of harmful but remediable factors contributing to pain undertreatment and inappropriate opioid prescribing, including [10]:

- Knowledge gaps in medical standards, current evidence-based outcomes, guidelines for appropriate pain treatment, and regulatory policies
- Prescriber concerns that legitimate opioid prescribing will lead to unnecessary scrutiny by regulatory authorities
- Conflicting information in existing clinical guidelines
- Prescriber concerns of patient deception to obtain drugs for abuse and fears of precipitating addiction

CHARACTERISTICS OF APPROPRIATE AND INAPPROPRIATE OPIOID PRESCRIBING	
Medically Legitimate Pain Management and Prescribing	**Inappropriate Pain Management and Prescribing**
Based on sound clinical judgment and current best clinical practices	Inadequate attention in initial assessment to clinical indication or patient risk of opioid problems
Appropriately documented	Inadequate monitoring
Demonstrable patient benefit	Inadequate patient education and informed consent
Occurs during the usual course of professional practice	Unjustified dose escalation without sufficient attention to risks or alternative treatments
A legitimate physician-patient relationship exists	Excessive reliance on opioids, especially high-dose opioids, for chronic pain
Prescribing or administration appropriate to diagnosis	Failure to use risk assessment tools
Careful follow-up monitoring of patient response and safe patient use	
Demonstration of adjustment to therapy, as needed	
Documentation of appropriate referrals, as necessary	
Source: [10]	*Table 8*

Prescribers were held to a standard of safe and best clinical practice, the general points of which include [10]:

- Prescribers should know best clinical practices in opioid prescribing, associated risks of opioids, assessment of pain and function, and pain management approaches. Pharmacologic and nonpharmacologic modalities should be used on the basis of current knowledge in the evidence base or best clinical practices.
- Pain should be assessed and treated promptly, with therapy selection based on the nature of the pain, treatment response, and patient risk level for developing opioid problems.
- Prescribers should use safeguards to minimize misuse and diversion risk of opioid analgesics.
- In allegations of inappropriate pain management, the Board will not take disciplinary action for deviation from "best practices" when medical records show reasonable cause for deviation.

The model policy additionally stated that physicians would not be sanctioned on the sole basis of medically legitimate opioid prescribing (***Table 8***).

In 2015, the FSMB appointed a workgroup to review and analyze the original policy document as well as other state and federal policies on the prescribing of opioids in pain treatment, including advisories issued by the CDC and the FDA [114]. In April 2017, the FSMB adopted the *Guidelines for the Chronic Use of Opioid Analgesics*, an update to the original model policy that includes recommendations identified by the workgroup. The stated goal of this document is to provide state medical and osteopathic boards with an updated guideline for assessing physician management of pain, so as to determine whether opioid analgesics are used in a manner that is both medically appropriate and in compliance with applicable state and federal laws and regulations [114].

The FSMB 2017 Guidelines communicate the message that pain management is an important area of patient care, integral to medical practice; and that opioid analgesics may be necessary for pain control. In order to implement best practices for responsible opioid prescribing, clinicians should understand the relevant pharmacologic and clinical issues in the use of opioid analgesics and should

obtain sufficient targeted continuing education and training on the safe prescribing of opioids and other analgesics as well as training in multimodal treatments. The Guidelines focus on the general overall safe and evidence-based prescribing of opioids and treatment of chronic, non-cancer pain, with the specific limitation and restriction that they do not operate to create any specific standard of care. A variety of strategies may be used to achieve the goals of the Guidelines, including the patient's level of pain, preferences of the clinician and the patient, available resources, and other concurrent issues. The Guidelines do not encourage the prescribing of opioids over other pharmacological and nonpharmacological means of treatment. Pain management should be viewed as essential to both the quality of medical practice and to the quality of life for patients who suffer from pain. The Guidelines are not intended for the treatment of acute pain, acute pain management in the perioperative setting, emergency care, cancer-related pain, palliative care, or end-of-life care. They apply most directly to the treatment of chronic pain lasting more than three months in duration or past the time of normal tissue healing [114].

ASSESSING OPIOID BENEFIT AND RISK OF MISUSE

In deciding whether to prescribe an opioid analgesic for chronic pain, clinicians should perform, and document in the record, an assessment of the potential benefits and risks to the patient. The elements of such an assessment include [114]:

- Pain indications for opioid therapy
- Nature and intensity of pain
- Past and current pain treatments and patient response
- Comorbid conditions
- Pain impact on physical and psychological function
- Social support, housing, and employment
- Home environment (i.e., stressful or supportive)
- Pain impact on sleep, mood, work, relationships, leisure, and substance use
- Patient history of physical, emotional, or sexual abuse

If there is a history of substance abuse, active or in remission, consult an addiction specialist before starting opioids [114]. In active substance abuse, do not prescribe opioids until the patient is engaged in a treatment/recovery program or other arrangement made, such as addiction professional co-management and additional monitoring. When considering an opioid analgesic (particularly ER or LA types), one must always weigh the benefits against the risks of overdose, abuse, addiction, physical dependence and tolerance, adverse drug interactions, and accidental ingestion by children [115].

RISK ASSESSMENT TOOLS

Risk assessment involves a determination of whether potential opioid benefits outweigh the potential risks. The individual and public health consequences of prescription opioid abuse, addiction, diversion, and overdose justify assessment and risk stratification in every patient considered for long-term opioid therapy [116]. Patients with chronic pain and past or current alcohol or drug abuse, psychiatric illness, or serious aberrant drug-related behaviors should still be considered for opioid therapy, but with tighter monitoring conditions and consultation from mental health or addiction specialists. Pain management outcomes are negatively affected by untreated psychiatric comorbidity, and proper assessment can identify and lead to the treatment of these conditions [117]. Periodic reassessment is necessary because patient circumstances and the benefit/risk balance of opioid therapy can change, due to alterations in the primary pain condition, comorbid disease, or psychological or social circumstances [116].

Before Opioid Therapy Initiation

Screening and assessment tools can help guide patient stratification according to risk level and inform the appropriate degree of structure and monitoring in the treatment plan. It should be noted that despite widespread endorsement of screening tool use to help determine patient risk level, most screening tools have not been extensively evaluated, validated, or compared to each other, and evidence of their reliability is poor [97; 118]. In addition to screening and assessment tools, urine drug testing, monitoring of prescribing practices, prescription monitoring programs, opioid treatment agreements, and utilization of universal precautions are essential. Presently, a combination of strategies is recommended to stratify risk, to identify and understand aberrant drug related behaviors, and to tailor treatments accordingly [119].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Interventional Pain Physicians recommends screening for opioid abuse, as it will potentially identify opioid abusers and reduce opioid abuse. (https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed August 21, 2020.)

Level of Evidence: II (Evidence obtained from at least one relevant, high-quality randomized controlled trial or multiple relevant moderate- or low-quality randomized controlled trials)

Opioid Risk Tool

The Opioid Risk Tool (ORT) is a five-item assessment to help predict aberrant drug-related behavior. It is also used to establish patient risk level through patient categorization into low, medium, or high levels of risk for aberrant drug-related behaviors based on responses to questions of previous alcohol/drug abuse, psychological disorders, and other risk factors [28].

Screener and Opioid Assessment for Patients with Pain–Revised

The Screener and Opioid Assessment for Patients with Pain–Revised (SOAPP-R) is a patient-administered, 24-item screen with questions addressing history of alcohol/substance use, psychologic status, mood, cravings, and stress. Like the ORT, the SOAPP-R helps assess risk level of aberrant drug-related behaviors and the appropriate extent of monitoring [120].

CAGE and CAGE-AID

The original CAGE (Cut down, Annoyed, Guilty, and Eye-opener) Questionnaire consists of four questions designed to help clinicians determine the likelihood that a patient is misusing or abusing alcohol. These same four questions were adapted to include drugs (CAGE-AID), and this tool may be used to assess the likelihood of current substance abuse [121].

Diagnosis, Intractability, Risk, Efficacy Tool

The Diagnosis, Intractability, Risk, Efficacy (DIRE) tool is a clinician-rated questionnaire used to predict patient compliance with long-term opioid therapy [122]. Patients scoring lower on the DIRE tool are poor candidates for long-term opioid analgesia.

Mental Health Screening Tool

The Mental Health Screening Tool is a five-item screen that asks about a patient's feelings of happiness, calmness, peacefulness, nervousness, and depression in the past month [123]. A lower score on this tool is an indicator that the patient should be referred to a specialist for pain management.

PATIENT RISK STRATIFICATION

Common to most clinical practice guidelines, and discussed in the FSMB 2017 Guidelines, is patient stratification by level of risk [114]. All practice guidelines for opioid analgesic prescribing recommend assessing the risk of misuse, abuse, or

PATIENT RISK STRATIFICATION
Low Risk
Definable physical pathology with objective signs and reliable symptoms
Clinical correlation with diagnostic testing including magnetic resonance imaging, physical examination, and interventional diagnostic techniques
With or without mild psychological comorbidity
With or without minor medical comorbidity
None or well-defined and controlled personal or family history of alcoholism or substance abuse
Age 45 years or older
High levels of pain acceptance and active coping strategies
High motivation, willingness to participate in multimodal therapy and attempting to function at normal levels
Medium Risk
Significant pain problems with objective signs and symptoms confirmed by radiological evaluation, physical examination, or diagnostic interventions
Moderate psychological problems, well-controlled by therapy
Moderate coexisting medical disorders well controlled by medical therapy and which are not affected by chronic opioid therapy such as central sleep apnea
Those who develop mild tolerance but not hyperalgesia without physical dependence or addiction
Past history of personal or family history of alcoholism or substance abuse
Pain involving more than three regions of the body
Defined pathology with moderate levels of pain acceptance and coping strategies
Willing to participate in multimodal therapy, attempting to function in their normal daily lives
High Risk
Widespread pain without objective signs and symptoms
Pain involving more than three regions of the body
Aberrant drug-related behavior
History of misuse, abuse, addiction, diversion, dependency, tolerance, and hyperalgesia
History of alcoholism
Major psychological disorders
Age younger than 45 years
HIV-related pain
High levels of pain exacerbation and low levels of coping strategies
Unwilling to participate in multimodal therapy; not functioning close to a near normal lifestyle
Source: [97] *Table 9*

addiction in all patients before initiating long-term (≥90 days) opioid therapy and in high-risk patients prior to acute pain therapy. Patient risk level is designated as low, medium, or high based on background and clinical characteristics (***Table 9***) [97].

Low-risk patients receive the standard level of monitoring, vigilance, and care. Moderate-risk patients should be considered for an additional level of monitoring and provider contact, and high-risk patients are likely to require intensive and structured monitoring and follow-up contact, additional consultation with psychiatric and addiction medicine specialists, and limited supplies of short-acting opioid formulations [21].

SAFETY PRECAUTIONS

A simplified approach to opioid prescribing safety, based on the core concept of universal precautions but designed with high specificity for opioid analgesics, was presented at the 2013 annual conference of the AAPM. The eight principles are specifically intended to reduce fatalities with opioid analgesic prescribing and are now incorporated in the AAPM Safe Opioid Prescribing Initiative [124]. They may be recalled using the acronym RELIABLE:

- **R**espiratory: If a patient on long-term opioids develops a respiratory condition (e.g., asthma, pneumonia, flu), reduce the opioid dose by 20% to 30%.
- **E**xperience: Assess the patient before prescribing opioids to explore biologic, social, and psychiatric risk factors.
- **L**ong-term: Extended-release opioids should not be used for acute pain.
- **I**nitiating methadone: Never start methadone at a dose ≥15 mg/day.
- **A**pnea: Screen for hypoxemia and obstructive or central sleep apnea, especially in patients who are taking 150 mg/day MED or who are obese, infirm, or elderly.
- **B**enzodiazepines: Avoid these agents if possible because they enhance opioid toxicity.
- **L**ook for comorbidities: Patients often misuse opioid analgesics for their mental health disorder instead of their pain, so assess patients for a history of bipolar disorder, post-traumatic stress disorder, depression, stress, and general anxiety disorder.
- **E**xercise caution with rotation: Conversion tables and equal analgesic tables should not be used to determine opioid starting doses. Assume everyone is opioid naïve, start on a low dose, and titrate slowly to the maximum dose one can safely prescribe.

DEVELOPING A SAFE OPIOID TREATMENT PLAN FOR MANAGING CHRONIC PAIN

As discussed, healthcare professionals should know best clinical practices in opioid prescribing, including the associated risks of opioids, approaches to the assessment of pain and function, and pain management modalities. Pharmacologic and nonpharmacologic approaches should be used on the basis of current knowledge in the evidence base or best clinical practices. Patients with moderate-to-severe chronic pain who have been assessed and treated, over a period of time, with non-opioid pharmacologic or nonpharmacologic pain therapy without adequate pain relief are considered to be candidates for a trial of opioid therapy. The treatment plan should always be individualized for the patient and begun as an "initial therapeutic trial" before embarking on a definitive course of treatment [114].

All patients with pain have a level of risk that can only be roughly estimated initially and modified over time as more information is obtained. There are ten essential steps of opioid prescribing for chronic pain to help mitigate any potential problems [114]:

- Diagnosis with an appropriate differential
- Psychologic assessment, including risk of substance use disorders
- Informed consent
- Treatment agreement
- Pre- and post-treatment assessments of pain level and function

- Appropriate trial of opioid therapy with or without adjunctive medication
- Reassessment of patient levels of pain and functioning
- Regular assessment with the 5 A's (i.e., analgesia, activity, adverse effects, aberrant behaviors, and affect)
- Periodically review pain diagnosis and comorbid conditions, including substance use disorders
- Documentation

INFORMED CONSENT AND TREATMENT AGREEMENTS

The initial opioid prescription is preceded by a written informed consent or "treatment agreement" [114]. This agreement should address potential side effects, tolerance and/or physical dependence, drug interactions, motor skill impairment, limited evidence of long-term benefit, misuse, dependence, addiction, and overdose. Informed consent documents should include information regarding the risk/benefit profile for the drug(s) being prescribed. The prescribing policies should be clearly delineated, including the number/frequency of refills, early refills, and procedures for lost or stolen medications [114].

The American Society of Interventional Pain Physicians asserts that a robust agreement, which is followed by all parties, is essential prior to initiating and maintaining opioid therapy, as such agreements reduce overuse, misuse, abuse, and diversion.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed August 21, 2020.)

Level of Evidence: III (Evidence obtained from at least one relevant, high-quality nonrandomized trial or observational study with multiple moderate- or low-quality observational studies)

The treatment agreement also outlines joint prescriber and patient responsibilities [114]. The patient agrees to using medications safely, refraining from "doctor shopping," and consenting to routine urine drug tests (UDTs). The prescriber's responsibility is to address unforeseen problems and prescribe scheduled refills. Reasons for opioid therapy change or discontinuation should be listed [114]. Agreements can also include sections related to follow-up visits, monitoring, and safe storage and disposal of unused drugs.

Considerations for Non-English-Proficient Patients

For patients who are not proficient in English, it is important that information regarding the risks associated with the use of opioids and available resources be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

INITIATING A TRIAL OF OPIOID THERAPY

Opioid therapy should be presented as a trial for a pre-defined period (usually no more than 30 days). The goals of treatment should be reasonable improvements in pain, function, depression, anxiety, and avoidance of unnecessary or excessive medication use [114]. The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies.

In opioid-naïve patients, start at the lowest possible dose and titrate to effect. Dosages for opioid-tolerant patients should always be individualized and titrated by efficacy and tolerability [114]. The need for frequent progress and benefit/risk assessments during the trial should be included in patient education. Patients should also have full knowledge of the warning signs and symptoms of respiratory depression.

Prescribers should be knowledgeable of federal and state opioid prescribing regulations. Issues of equianalgesic dosing, close patient monitoring during all dose changes, and cross-tolerance with opioid conversion should be considered. If necessary, treatment may be augmented, with preference for nonopioid and immediate-release opioids over ER/LA opioids. Taper opioid dose when no longer needed [115].

PERIODIC REVIEW AND MONITORING

When implementing a chronic pain treatment plan that involves the use of opioids, the patient should be frequently reassessed for changes in pain origin, health, and function [114]. This can include input from family members and/or the state prescription drug monitoring program (PDMP) [114]. During the initiation phase and during any changes to the dosage or agent used, patient contact should be increased. At every visit, chronic opioid response may be monitored according to the 5 A's [10]:

- Analgesia
- Activities of daily living
- Adverse or side effects
- Aberrant drug-related behaviors
- Affect (i.e., patient mood)

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Interventional Pain Physicians recommends monitoring for side effects (e.g., constipation) and managing them appropriately, including discontinuation of opioids when indicated. (https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed August 21, 2020.)

Level of Evidence: I (Evidence obtained from multiple relevant high quality randomized controlled trials for effectiveness)

Assessment During Ongoing Opioid Therapy

Signs and symptoms that, if present, may suggest a problematic response to the opioid and interference with the goal of functional improvement include [125]:

- Excessive sleeping or days and nights turned around
- Diminished appetite
- Inability to concentrate or short attention span
- Mood volatility, especially irritability
- Lack of involvement with others
- Impaired functioning due to drug effects
- Use of the opioid to regress instead of re-engaging in life
- Lack of attention to hygiene and appearance

The decision to continue, change, or terminate opioid therapy is based on progress toward treatment objectives and absence of adverse effects and risks of overdose or diversion [114]. Satisfactory therapy is indicated by improvements in pain, function, and quality of life. Brief assessment tools to assess pain and function may be useful, as may UDTs. Treatment plans may include periodic pill counts to confirm adherence and minimize diversion.

VIGIL

VIGIL is the acronym for a five-step risk management strategy designed to empower clinicians to appropriately prescribe opioids for pain by reducing regulatory concerns and to give pharmacists a framework for resolving ambiguous opioid analgesic prescriptions in a manner that preserves legitimate patient need while potentially deterring diverters. The components of VIGIL are [126]:

- **V**erification: Is this a responsible opioid user?
- **I**dentification: Is the identity of this patient verifiable?
- **G**eneralization: Do we agree on mutual responsibilities and expectations?
- **I**nterpretation: Do I feel comfortable allowing this person to have controlled substances?
- **L**egalization: Am I acting legally and responsibly?

The foundation of VIGIL is a collaborative prescriber/pharmacist relationship [127; 128].

Current Opioid Misuse Measure

The Current Opioid Misuse Measure (COMM) is a 17-item patient self-report assessment designed to help clinicians identify misuse or abuse in patients with chronic pain. Unlike the ORT and the SOAPP-R, the COMM identifies aberrant behaviors associated with opioid misuse in patients already receiving long-term opioid therapy [21]. Sample questions include: In the past 30 days, how often have you had to take more of your medication than prescribed? In the past 30 days, how much of your time was spent thinking about opioid medications (e.g., having enough, taking them, dosing schedule)?

Pain Assessment and Documentation Tool

Guidelines by the FSMB and the Joint Commission stress the importance of documentation from both a healthcare quality and medicolegal perspective. Research has found widespread deficits in chart notes and progress documentation with patients with chronic pain receiving opioid therapy, and the Pain Assessment and Documentation Tool (PADT) was designed to address these shortcomings [129]. The PADT is a clinician-directed interview, with most sections (e.g., analgesia, activities of daily living, adverse events) consisting of questions asked of the patient. However, the potential aberrant drug-related behavior section must be completed by the physician based on his or her observations of the patient.

The Brief Intervention Tool

The Brief Intervention Tool is a 26-item, "yes-no," patient-administered questionnaire used to identify early signs of opioid abuse or addiction. The items assess the extent of problems related to drug use in several areas, including drug use-related functional impairment [123].

Involvement of Family Members

Family members of the patient can provide valuable information that better informs decision making regarding continuing opioid therapy. Family members can observe whether a patient is losing control of his or her life or becoming less functional or more depressed during the course of opioid therapy. They can also provide input regarding positive or negative changes in patient function, attitude, and level of comfort. The following questions can be asked of family members or a spouse to help clarify whether the patient's response to opioid therapy is favorable or unfavorable [125]:

- Is the person's day centered around taking the opioid medication? Response can help clarify long-term risks and benefits of the medication and identify other treatment options.

MONITORING FREQUENCY ACCORDING TO PATIENT RISK			
Monitoring Tool	**Patient Risk Level**		
	Low	**Medium**	**High**
Urine drug test	Every 1 to 2 years	Every 6 to 12 months	Every 3 to 6 months
State prescription drug monitoring program	Twice per year	3 times per year	4 times per year

Source: [130] *Table 10*

- Does the person take pain medication only on occasion, perhaps three or four times per week? If yes, the likelihood of addiction is low.
- Have there been any other substance (alcohol or drug) abuse problems in the person's life? An affirmative response should be taken into consideration when prescribing.
- Does the person in pain spend most of the day resting, avoiding activity, or feeling depressed? If so, this suggests the pain medication is failing to promote rehabilitation. Daily activity is essential, and the patient may be considered for enrollment in a graduated exercise program.
- Is the person in pain able to function (e.g., work, do household chores, play) with pain medication in a way that is clearly better than without? If yes, this suggests the pain medication is contributing to wellness.

Urine Drug Testing

UDTs may be used to monitor adherence to the prescribed treatment plan and to detect unsanctioned drug use [114]. They should be used more often in patients receiving addiction therapy, but clinical judgment is the ultimate guide to testing frequency (***Table 10***) [130]. High-quality evidence supporting the benefits of UDTs in improving patient care are lacking, as much of the existing evidence comes from industry-sponsored studies that can portray a biased perspective, usually by stressing the prevalence of aberrant behaviors in patients who then require more frequent UDT monitoring [131].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Society of Interventional Pain Physicians, presumptive urine drug testing should be implemented at initiation of opioid therapy, along with subsequent use as adherence monitoring, using in-office point of service testing, followed by confirmation with chromatography/mass spectrometry for accuracy in select cases, to identify patients who are noncompliant or abusing prescription drugs or illicit drugs. Urine drug testing may decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed August 21, 2020.)

Level of Evidence: III (Evidence obtained from at least one relevant, high-quality nonrandomized trial or observational study with multiple moderate- or low-quality observational studies)

Initially, testing involves the use of class-specific immunoassay drug panels [10]. If necessary, this may be followed with gas chromatography/mass spectrometry for specific drug or metabolite detection. It is important that testing identifies the specific drug rather than the drug class, and the prescribed opioid should be included in the screen. Any abnormalities should be confirmed with a laboratory toxicologist or clinical pathologist. Immunoassay may be used point-of-care for "on-the-spot" therapy changes, but the high error rate prevents its use in major clinical decisions unless liquid chromatography is coupled with mass spectrometry confirmation.

Urine test results suggesting opioid misuse should be discussed with the patient using a positive, supportive approach. The test results and the patient discussion should be documented.

Ethical Concerns with UDTs

It is important to appreciate the limitations of UDTs. Healthcare providers are increasingly relying on UDTs as a means to reduce abuse and diversion of prescribed opioids. This has led to a proliferation in diagnostic laboratories that offer urine testing. With this increase have come questions of whether these business interests benefit or hinder patient care, what prescribers should do with the information they obtain, the accuracy of urine screens, and whether some companies and clinicians are financially exploiting the UDT boom [131]. A random sample of UDT results from 800 patients with pain treated at a Veterans Affairs facility found that 25.2% were negative for the prescribed opioid and 19.5% were positive for an illicit drug/unreported opioid [132]. However, a negative UDT result for the prescribed opioid does not necessarily indicate diversion; it may indicate the patient halted its use due to side effects, lack of efficacy, or pain remission. The increasingly stringent climate surrounding clinical decision-making regarding aberrant UDTs is concerning. In many cases, a negative result for the prescribed opioid or a positive UDT serves as the pretense to terminate a patient rather than an impetus to guide him or her into addiction treatment or an alternative pain management program [131].

In principle, and ideally in practice, UDTs are a worthwhile element of effective pain management and pharmacovigilance when used to enhance the diagnostic and therapeutic objectives of pain therapy. However, when UDT use is motivated by fear, coercion, or profiteering, patients may be offended or feel intimidated by the practice [131].

As a side note, cannabis use by patients with chronic pain receiving opioid therapy has traditionally been viewed as a treatment agreement violation that is grounds for termination of opioid therapy. However, some now argue against cannabis use as a rationale for termination or substantial treatment and monitoring changes, especially considering the increasing legalization of medical use at the state level [25].

PATIENT AND CAREGIVER EDUCATION

Safe Use of Opioids

Patients and caregivers should be counseled regarding the safe use and disposal of opioids. As part of its mandatory Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioids, the FDA has developed a patient counseling document with information on the patient's specific medications, instructions for emergency situations and incomplete pain control, and warnings not to share medications or take them unless prescribed [115]. A copy of this form may be accessed online at https://www.fda.gov/media/86281/download.

When prescribing opioids, clinicians should provide patients with the following information and instructions [115]:

- Product-specific information
- Taking the opioid as prescribed
- Importance of dosing regimen adherence, managing missed doses, and prescriber contact if pain is not controlled
- Warning and rationale to never break or chew/crush tablets or cut or tear patches prior to use
- Warning and rationale to avoid other central nervous system (CNS) depressants, such as sedative-hypnotics, anxiolytics, alcohol, or illicit drugs
- Warning not to abruptly halt or reduce the opioid without physician oversight of safe tapering when discontinuing

- The potential of serious side effects or death
- Risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions
- The risks of falls, using heavy machinery, and driving
- Warning and rationale to never share an opioid analgesic
- Rationale for secure opioid storage
- Warning to protect opioids from theft
- Instructions for disposal of unneeded opioids, based on product-specific disposal information

Disposal of Opioids

There are no universal recommendations for the proper disposal of unused opioids, and patients are rarely advised of what to do with unused or expired medications [133]. According to the Office of National Drug Control Policy, most medications that are no longer necessary or have expired should be removed from their containers, mixed with undesirable substances (e.g., cat litter, used coffee grounds), and put into an impermeable, nondescript container (e.g., disposable container with a lid or a sealed bag) before throwing in the trash [134]. Any personal information should be obscured or destroyed. The FDA recommends that certain medications, including oxycodone/acetaminophen (Percocet), oxycodone (OxyContin tablets), and transdermal fentanyl (Duragesic Transdermal System), be flushed down the toilet instead of thrown in the trash [134]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so.

The American College of Preventive Medicine has established the following best practices to avoid diversion of unused drugs and educate patients regarding drug disposal [133]:

- Consider writing prescriptions in smaller amounts.
- Educate patients about safe storing and disposal practices.
- Give drug-specific information to patients about the temperature at which they should store their medications. Generally, the bathroom is not the best storage place. It is damp and moist, potentially resulting in potency decrements, and accessible to many people, including children and teens, resulting in potential theft or safety issues.
- Ask patients not to advertise that they are taking these types of medications and to keep their medications secure.

Refer patients to community "take back" services overseen by law enforcement that collect controlled substances, seal them in plastic bags, and store them in a secure location until they can be incinerated. Contact your state law enforcement agency or visit https://www.dea.gov to determine if a program is available in your area.

CONSULTATION AND REFERRAL

It is important to seek consultation or patient referral when input or care from a pain, psychiatry, addiction, or mental health specialist is necessary. Clinicians who prescribe opioids should become familiar with opioid addiction treatment options (including licensed opioid treatment programs for methadone and office-based opioid treatment for buprenorphine) if referral is needed [114].

Ideally, providers should be able to refer patients with active substance abuse who require pain treatment to an addiction professional or specialized program. In reality, these specialized resources are scarce or non-existent in many areas [114]. Therefore, each provider will need to decide whether the risks of continuing opioid treatment while a patient is using illicit drugs outweigh the benefits to the patient in terms of pain control and improved function [25].

MEDICAL RECORDS

Documentation is a necessary aspect of all patient care, but it is of particular importance when opioid prescribing is involved. All clinicians should maintain accurate, complete, and up-to-date medical records, including all written or telephoned prescription orders for opioid analgesics and other controlled substances, all written instructions to the patient for medication use, and the name, telephone number, and address of the patient's pharmacy [114]. Good medical records demonstrate that a service was provided to the patient and that the service was medically necessary. Regardless of the treatment outcome, thorough medical records protect the prescriber.

DISCONTINUING OPIOID THERAPY

The decision to continue or end opioid prescribing should be based on a joint discussion of the anticipated benefits and risks. An opioid should be discontinued with resolution of the pain condition, intolerable side effects, inadequate analgesia, lack of improvement in quality of life despite dose titration, deteriorating function, or significant aberrant medication use [114].

Clinicians should provide physically dependent patients with a safely structured tapering protocol. Withdrawal is managed by the prescribing physician or referral to an addiction specialist. Patients should be reassured that opioid discontinuation is not the end of treatment; continuation of pain management will be undertaken with other modalities through direct care or referral.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Interventional Pain Physicians recommends advising patients undergoing dosage titration in a trial of opioid therapy to avoid engaging in dangerous activities, such as driving a motor vehicle or the use of heavy machinery, until a stable dosage is established and it is certain that the opioid dose does not cause sedation, as well as when taking opioids with alcohol, benzodiazepines, or other sedating drugs.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed August 21, 2020.)

Level of Evidence: Expert Opinion/Consensus Statement

Level of Evidence: I (Evidence obtained from multiple relevant high quality randomized controlled trials for effectiveness)

COMPLIANCE WITH FEDERAL AND STATE LAWS

OPIOID RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

In response to the rising incidence in prescription opioid abuse, addiction, diversion, and overdose since the late 1990s, the FDA has mandated opioid-specific REMS to reduce the potential negative patient and societal effects of prescribed opioids. Another element of opioid risk mitigation is FDA partnership with other governmental agencies, state professional licensing boards, and societies of healthcare professionals to help improve prescriber knowledge of appropriate and safe opioid prescribing and safe home storage and disposal of unused medication [125].

FDA AMENDMENTS ACT OF 2007

The FDA Amendments Act (FDAAA) of 2007 gave the FDA authority to require REMS from manufacturers to ensure that benefits of a drug or biological product outweigh risks. REMS replaced the previously existing risk management programs, termed Risk Minimization Action Plans (RiskMAPs). An important distinction between the two programs is that the FDA did not have authority to require or enforce a RiskMAP after product approval. The FDA now has the authority to require REMS as part of the approval process for a new medication or post-approval if the agency becomes aware of new safety information pertaining to serious medication-associated risks following approval for marketing [115].

As defined by the FDAAA, REMS may include a medication guide, a patient education package insert, a communication plan, and other elements to assure safe use (ETASUs). ETASUs must address the goals to mitigate a specific serious risk listed in the labeling of the drug and may include [115]:

- Prescriber training, experience, or certification
- Distributor or dispenser training or certification
- Restricted distribution or dispensing
- Dispensing limited to patients with evidence of safe use conditions, such as laboratory test results
- Patient monitoring
- Patient enrollment in a registry
- Physician and/or pharmacist enrollment in a registry

The FDA maintains a list of current opioid analgesic REMS at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

SPECIFIC OPIOIDS WITH A REMS REQUIREMENT

In 2011, the FDA announced the components of REMS that would apply to all ER/LA opioid formulations. The decision to not include short-acting formulations was based on the substantially greater opioid amount in ER/LA formulations and the corresponding greater risk of serious adverse outcomes, including fatality, when taken by someone for whom they were not prescribed, by patients who succeed in defeating the delayed-release mechanism, or by any user co-ingesting alcohol, benzodiazepines, or other respiratory suppressant substances. Primary elements of the ER/LA REMS include changes in product labeling and the requirement that all ER/LA opioid formulation manufacturers provide specific information to prescribers and patients [135]. For example, there is a new indication for all ER/LA opioids that the pain must be severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. The original indication for the treatment of "moderate" pain was eliminated. In addition, the distinctions between cancer pain and chronic noncancer pain were removed. Prescriber education regarding ER/LA opioids is provided through accredited continuing education activities supported by independent educational grants from ER/LA opioid analgesic companies. This includes guidance regarding patient education on the risks and benefits of ER/LA opioid analgesics.

In 2012, the FDA issued a class-specific REMS for all transmucosal immediate-release fentanyl (TIRF) opioid products. Training was required for all prescribers, pharmacies, distributors, and outpatients who prescribed, dispensed, or received TIRF products [136].

ABUSE-DETERRENT OPIOID FORMULATIONS

Drug developers, manufacturers, and regulatory bodies face daunting challenges in formulating and implementing strategies to reduce the abuse, addiction, diversion, and overdose of prescription opioids. One challenge has been to identify and manufacture analgesics effective in the treatment of severe pain that also possess minimal abuse liability. These products must provide full analgesia with low "opioid attractiveness" to persons intent on abusing or diverting the drug; this strategy is consistent with the opioid REMS principle of drug benefit outweighing risk [137]. The development of abuse-deterrent formulations (ADFs) was also an approach to help avoid the unintended harms to patients with legitimate pain observed in Washington and Florida, where imposition of opioid prescribing restrictions were found to discourage legitimate treatment of chronic pain while making little or no impact on opioid analgesic abuse and diversion [138]. Although ADF opioids retain some abuse liability if used inappropriately or combined with other substances, most ADFs are now being developed to prevent defeat of the delayed-release mechanism or use through illicit routes of administration [139; 140].

Helping to prompt the development of ADF opioids were reports that as many as 80% of prescription opioid abusers in drug rehabilitation tampered with ER opioid formulations [141]. Strategies used by opioid abusers to disable the delayed-release mechanism to accelerate drug release include crushing and swallowing; crushing and snorting; crushing and smoking; or crushing, dissolving, and injecting. The FDA states that ADFs should target known or expected routes of abuse for the opioid constituent in the given formulation [142].

ADVANTAGES AND DISADVANTAGES OF DIFFERENT ADF STRATEGIES

Several ADF opioids have received approval for marketing in the United States; others are in the process of evaluation, and one ADF was released for marketing and subsequently recalled by the manufacturer [138]. These formulations use different strategies to prevent misuse, with varying advantages and disadvantages (***Table 11***) [138].

While all ADF strategies may potentially deter tampering, physical barriers to crushing or chewing appear to be the only strategy that benefits nonabusers and abusers alike by preventing accidental crushing or chewing and not inducing adverse events. This contrasts with strategies that precipitate adverse events to deter inappropriate use, such as ADFs that use sequestered aversive agents that will induce adverse events in patients who chew or crush the tablets, accidentally or without intent of abuse. The extent of deterrence from these formulations is unclear because some persons are willing to endure discomfort from the aversive agent in order to obtain the more intense high from tampering. Sequestered opioid antagonists may offer a more effective approach in pharmacologic abuse deterrence by rendering the opioid ineffective, but they can induce sudden and severe opioid withdrawal in physically dependent patients who accidentally chew the tablet [138].

ADF OUTCOME DATA

Although opioid ADFs have been introduced into widespread clinical use relatively recently, several studies of their efficacy have already been published. These reports have documented significantly reduced abuse rates of ADF opioids after they have fully replaced the original formulations, but no effect on the overall rates of opioid abuse. For example, data were obtained on 140,496 persons assessed for substance abuse treatment, spanning from one year before ADF OxyContin (Oxy ADF) introduction to two years post-Oxy ADF introduction. Abuse of OxyContin was 41% lower with the ADF versus the original formulation, including a

ADVANTAGES AND DISADVANTAGES OF ADF STRATEGIES		
ADF Strategy	**Advantages**	**Disadvantages**
Physical barriers	Prevents crushing or chewing to block rapid high-dose opioid release into the system Prevents accidental crushing or chewing in compliant patients No adverse events in compliant patients FDA-approved formulation available	Does not deter abuse of intact tablets Only one FDA-approved product available
Aversive components (e.g., niacin)	May prevent abuse by chewing or crushing the product May limit abuse of intact tablets because taking too much will amplify adverse events	Potential adverse events in compliant patients taking product as intended Adverse events with intact tablets may prevent legitimate dose increase if pain increases or efficacy decreases over time Adverse events may not be sufficient to deter a motivated abuser No FDA-approved formulations
Sequestered antagonist (e.g., naloxone, naltrexone)	Prevents abuse by chewing or crushing opioids FDA-approved formulation available	Does not deter abuse of intact tablets Chewing or crushing the tablet may trigger severe withdrawal symptoms
Source: [138]		*Table 11*

17% decrease in oral abuse and a 66% decrease in abuse through non-oral routes. Meaningful reductions in ER morphine and ER oxymorphone abuse rates were not found. The authors concluded that conversion of OxyContin to an ADF formulation was successful in reducing non-oral administration that requires tampering [143]. Another study found that following OxyContin ADF introduction, poison center exposures for oxycodone ER abuse declined 38% per population and 32% per unique recipients of dispensed drug. Therapeutic error exposures declined 24% per population and 15% per unique recipients of dispensed drug, and diversion reports declined 53% per population and 50% per unique recipients of dispensed drug. The declines were greater than those observed for other prescription opioids in aggregate [144]. However, several published reports have documented the abandonment of opioid analgesics and a migration to heroin use by previous OxyContin abusers following the introduction of ADF OxyContin [145; 146].

REGULATORY MANDATES

The FDA has prohibited labeling or marketing claims of abuse resistance or abuse deterrence to be used in any ADF opioid product because supportive epidemiologic data have not yet been published [147]. Any future label claim of abuse deterrence must be supported by post-marketing data [138].

In 2013, Purdue Pharma and Endo Pharma, the makers of OxyContin and Opana ER, respectively, requested a ruling from the FDA that the original formulations were removed from market and replaced by ADFs because of safety or efficacy concerns. Such a ruling would render the original formulations ineligible for generic replication, thus protecting ADF OxyContin and Opana ER market share from generic non-ADF competition [148]. The FDA ruled in favor of this request for Purdue but not for Endo. The basis for the decision was the extent of abuse liability with the original OxyContin preparation and insufficiency in the abuse deterrence with the ADF formulation to block

future applications to produce generic versions of the non-ADF Opana ER [149]. Interestingly, this favorable ruling for Purdue Pharma was made on April 16, 2013, the exact date of patent expiration for OxyContin [148].

In 2013, the FDA issued a draft document to guide pharmaceutical companies in developing ADF opioid products. Although the FDA strongly encourages industry to employ ADFs in new opioid products, the guidance document fell short of a mandate [142]. Later that year, the FDA approved an ER formulation of hydrocodone (Zohydro) that lacks abuse-deterrent properties, which seemed contradictory to the FDA stance on ADF product development [150].

In June 2017, the FDA requested that Endo Pharma remove the reformulated Opana ER from the market based on concerns that the benefits of the drug may no longer outweigh the risks [151]. This is the first time the FDA has taken steps to remove a currently marketed opioid pain medication. The agency's decision was based on a review of available postmarketing data, which demonstrated a significant shift in the route of abuse of Opana ER from nasal to injection following release of the ADF formulation. Injection abuse of reformulated Opana ER has been associated with a serious outbreak of HIV and hepatitis C and with cases of thrombotic microangiopathy [151].

OTHER GOVERNMENT AND INDUSTRY EFFORTS

In response to increasing rates of opioid analgesic abuse, addiction, diversion, and overdose, the National Drug Control Policy created a multiagency Drug Abuse Prevention Plan in 2011 to reduce prescription drug abuse. The four key elements of the plan are expansion of PDMPs; responsible disposal of unused medications; reduction of pill mills through enhanced law enforcement efforts; and support for provider and patient education. Regarding provider education, several state medical boards (e.g., California, West Virginia) require prescribers to obtain continuing education credit in pain management and prescription opioid use [152].

As noted, emerging trends and patterns of prescription opioid abuse, addiction, and overdose are monitored by several industry and government agencies through data collection from a variety of sources, including health insurance claims; the Automation of Reports and Consolidated Orders System (ARCOS), a DEA-run program that monitors the flow of controlled substances from manufacturing through distribution to retail sale or dispensing; the Treatment Episode Data Set (TEDS), which monitors treatment admissions; National Center for Health Statistics state mortality data; and the Researched, Abuse, Diversion and Addiction-Related Surveillance (RADARS) System, which monitors prescription drug abuse, misuse, and diversion [153].

The DEA is responsible for formulating federal standards for the handling of controlled substances. In 2011, the DEA began requiring every state to implement electronic databases that track prescribing habits, referred to as PDMPs. Specific policies regarding controlled substances are administered at the state level [154].

Almost all states have enacted PDMPs to facilitate the collection, analysis, and reporting of information on controlled substances prescribing and dispensing. Most PDMPs employ electronic data transfer systems that transmit prescription information from the dispensing pharmacy to a state agency [114].

The General Accounting Office evaluated the efficacy of PDMPs and concluded that such programs have the potential to help law enforcement and regulatory agencies rapidly identify and investigate activities that may involve illegal prescribing, dispensing, or consumption of controlled substances. In states that have made real-time data available, PDMPs can help reduce prescription drug abuse and diversion by allowing prescribers to access

and detect whether a patient has been receiving multiple prescriptions for controlled substances or whether a patient has filled or refilled an order for a prescribed opioid [114]. However, several concerns over PDMPs were voiced around the time of their widespread introduction, including the risk that PDMPs may negatively affect patients with legitimate opioid need by reducing opioid prescribing, potential privacy issues, and more frequent physician visits [155].

REGULATIONS AND PROGRAMS AT THE STATE LEVEL

Several regulations and programs at the state level have been enacted in an effort to reduce prescription opioid abuse, diversion, and overdose, including [156]:

- Physical examination required prior to prescribing
- Tamper-resistant prescription forms
- Pain clinic regulatory oversight
- Prescription limits
- Prohibition from obtaining controlled substance prescriptions from multiple providers
- Patient identification required before dispensing
- Immunity from prosecution or mitigation at sentencing for individuals seeking assistance during an overdose

UNINTENDED NEGATIVE CONSEQUENCES OF EFFORTS TO REDUCE PRESCRIBED OPIOID MISUSE, DIVERSION, AND OVERDOSE

The United States is unquestionably experiencing serious substance abuse problems involving prescription opioids. Although efforts to curtail opioid analgesic prescribing and distribution have been well intentioned, several of the approaches have resulted in unintended consequences.

DIFFICULTY OBTAINING LEGITIMATE OPIOID ANALGESICS

Enactments of restrictive mandates to govern opioid analgesic prescribing and dispensing have created difficulty for patients in accessing legitimate opioid therapeutics. This has been especially well documented in the state of Washington, but it is highly prevalent in general. Concerns have been voiced by numerous key opinion leaders and prominent individuals in the pain treatment profession and community in an effort to draw attention to regulatory and law enforcement overreach at the expense of patients suffering in pain who require access to opioid analgesics.

One example is Jan Chambers, president of the National Fibromyalgia and Chronic Pain Association (NFMCPA). For incorporation into a position paper on patient rights to access pain medication, Chambers sought input from members requiring prescribed opioids for their pain condition. In the open letter encouraging member input, Chambers expressed concern over federal law enforcement and regulatory overreach involving heightened scrutiny of prescription filing and dispensing. Mandates cited as especially harmful were patient-prescriber opioid contracts required to specify a single pharmacy, a 30-day maximum supply of opioids and no refills, and prohibition of faxing or phoning opioid prescriptions to a pharmacy. Also

mentioned was the increasing rate of pharmacy refusal to dispense opioids, the result of greater pressures imposed by the DEA on pharmacy networks to obtain additional patient information to verify legitimacy. These pharmacy networks, in turn, have transferred this burden to individual pharmacists, who, similar to prescribers, have become fearful of attracting DEA scrutiny over opioid prescription dispensing. The end result has been difficulty finding a pharmacy to fill opioid prescriptions [157].

Similar concerns over negative unintended patient impact were communicated by Amy Abernethy, president of the American Academy of Hospice and Palliative Medicine (AAHPM) to the National Conference of Insurance Legislators (NCOIL). NCOIL is an organization of state legislators involved in insurance legislation and regulation, and her response concerned several recommendations in a proposed set of best practices guidelines to reduce opioid abuse that were released by NCOIL in 2013. Strategies included in the NCOIL draft were those already implemented at the state level that led to measurable reductions in abuse and overdose. Abernethy countered by arguing that the narrow measure of success came at the expense of patients and providers [158].

With a shortage of pain medicine specialists in the United States, most chronic pain care is provided at the primary care level, and in some states (e.g., Washington), many primary care practices display signs in offices stating they no longer prescribe opioids. Interestingly, a small number of primary care physicians have chosen to transform their practices into cash-only entities and charge very high fees for what amounts to the sole prescribing of opioid analgesics. Patients requiring opioids to maintain pain control and quality of life are forced to seek treatment from these physicians because many others have become intimidated by the new legislation [5].

PATIENTS WHO REQUIRE ULTRA-HIGH-DOSE OPIOIDS

An element of the backlash against escalating opioid prescribing and associated problems has been intense lobbying by some pain professionals to impose pre-established dose ceiling on opioid prescribing, such that a maximum daily dosage cannot be exceeded. Prominent among these groups has been Physicians for Responsible Opioid Prescribing (PROP) and the advocacy group Public Citizen. The imposition of a 100-mg MED maximum daily ceiling and a maximum prescribing duration of 90 consecutive days was requested for noncancer pain. The groups cited observational study findings of a correlational relationship between prescribed opioid dose and overdose risk as evidence, but these recommendations were rejected by the FDA [159].

Despite FDA rejection of a mandate for daily dose ceilings, many practitioners believe that high-dose prescribing is irresponsible and without medical legitimacy. This view was disseminated and seemingly legitimized by the 2009 opioid prescribing guidelines published by the APS and the AAPM, which stated that no existing evidence supports daily opioid doses ≥200 mg MED [116]. The validity of these assertions has been undermined by several findings of differences between patients in the opioid dose necessary to achieve sufficient pain control, which can vary 40-fold for the same clinical condition [160]. While ultra-high-dose opioid prescribing remains controversial, a small subset of patients do require massive doses of opioids for chronic pain. Authors and guidelines statements of the contrary are based on opinion without empirical support [161].

Patients with chronic pain who require ultra-high-dose opioids, in some cases more than 2,000 mg/day MED, are likely to be labeled as addicts or abusers by healthcare professionals and family members alike. In general, these patients are profoundly ill, impaired, and/or bed- or house-bound due to severe unremitting pain refractory to analgesic efforts using lower-dose opioids. The reason some patients

require ultra-high opioid doses remains unclear, but it is very likely that some, and perhaps the majority, possess a cytochrome P450 polymorphism or other genetic abnormality [162].

Patients with chronic pain who legitimately require ultra-high-dose opioids also require supplemental management considerations in addition to those applied to all patients with chronic pain prescribed opioids. Patients and their caregivers should receive education on recognizing overmedication and overdose and what to do if these occur, especially before tolerance has developed. Patients should be restricted from use of benzodiazepines, muscle relaxants, sedatives, and any other potential respiratory depressant medication. While not used in most pain medicine settings, blood levels of opioids have value when a significant discrepancy is observed between prescribed dose and apparent drug effect; serum level results can suggest metabolic variation that impacts opioid dose-response. Serum opioid level testing in these patients can also establish baseline for comparison against future tests. In the unfortunate event of patient death while receiving ultra-high-dose opioids, documenting high serum opioid level while the patient was ambulatory and functional can defend the prescriber against accusation of responsibility for the patient's overdose death when coroner findings reveal high serum opioid levels in the absence of other explanatory findings [161].

Some complications are highly probable with ultra-high-dose opioid therapy that may not occur with lower doses. Endocrine suppression is likely to occur, with testosterone suppression possible in men and some women. Sudden suppression of adrenal corticoids in an opioid-maintained patient manifests in nausea, weakness, and a drop in blood pressure. For these patients, hormone replacement is necessary if opioids remain essential for pain control. Movement and physical exercises are strongly recommended. Almost without exception, patients who require ultra-high opioid dosages have been too ill to engage in normal social or family functions and usually require resocialization counseling for guidance and motivation to resocialize and begin a new quality of life [161].

LAW ENFORCEMENT TACTICS

Activities by the DEA to curb prescription opioid abuse and diversion have been identified in particular as potentially excessive and inappropriate. The U.S. Congress has pressured the DEA to reduce the diversion of prescribed opioids, which the DEA initially achieved through the successful raiding and closure of many pill mills and rogue Internet pharmacies. The focus of the agency has now shifted to reducing opioid supply by targeting wholesalers and pharmacies within the legitimate supply chain. Many complaints have centered on DEA use of tactics identical to those use in combating illegal drug cartels, such as wiretaps, undercover operations, and informants. Retail and wholesale pharmacies raided by DEA tactical squads have complained of being treated as if they were armed criminal organizations [163].

The DEA has accelerated the use of audits and inspections to identify and sanction drug wholesalers, levying millions of dollars in fines for what it has claimed were violations of the law. In 2012, the DEA suspended the license of drug wholesaler Cardinal Health, Inc., prohibiting opioid analgesic sales from its central Florida center. The DEA rationale was failure to detect suspicious order volume from several of Cardinal Health's pharmacy customers. Numerous Walgreens and CVS pharmacies and distribution centers were also raided [163].

The DEA has justified their tactics on the basis of Congressional pressure to contain opioid diversion, with agency success measured by disruption and destruction of organizations and networks feeding the problem. However, John Burke, president of the nonprofit National Association of Drug Diversion Investigators (NADDI), stated that DEA behavior reflects a mindset that retail and wholesale pharmacies comprise an enemy requiring containment. Concerns have been raised over the

potential of DEA activity to adversely and negatively impact legitimate medical practice. This has led several congressional members to request that the Government Accountability Office investigate the effect of DEA conduct on medication shortages for patients with pain [163].

Actions of the DEA have produced widespread fear among prescribers and retail pharmacists regarding the prescribing or dispensing of opioids. In some localities, pharmacists greatly restrict dispensing opioids by refusing to fill prescriptions paid for in cash, from customers not well known to them, or from customers from certain geographic areas. Other pharmacy chains have stopped filling opioid prescriptions from higher-volume opioid prescribers. Prescribers report feeling burdened by mandates to tighten patient monitoring by increasing UDTs, documentation, and pill counts [163].

The DEA is also tasked with the oversight and control of ingredients allocated to drug manufacturers for drug production that are deemed an abuse liability. This task is performed annually and is based on manufacturer projection of legitimate patient needs. Manufacturers of drug products with abuse liability complain of DEA failure to authorize sufficient materials for adequate customer supply, which the DEA defends as resulting from poor business decisions by the manufacturers. This has contributed to patient inability to access needed prescribed opioids [163].

INCREASE IN HEROIN USE

Of great concern is the likelihood that persons addicted to prescription opioids will switch to heroin if their preferred opioid becomes difficult to obtain or extract from ADF opioid preparations. Some experts predicted a resurgence of heroin abuse and fatal overdose, largely driven by opioid analgesic prescribing restrictions and by replacement of some opioid preparations by ADFs [164; 165; 166].

Statistics seem to bear this out. In 2014, the percentage of prescription opioid abuse was lower than the percentages in most years from 2002 to 2012 (although similar to the percentage in 2013) [166]. At the same time, heroin use increased. In 2014, the estimates of both current and past heroin use were higher than the estimates for most years between 2002 and 2013 [167]. In addition, first-time past-year use nearly doubled between 2006 and 2012 [168]. Past-year heroin initiation rose sharply in all regions in the United States, except the South. Unfortunately, the data do not provide estimates of patients with chronic pain resorting to heroin use when their opioid analgesic prescriptions are decreased or discontinued.

One study examined the impact of ADF OxyContin introduction on the abuse of OxyContin and other opioids. Researchers analyzed the results of surveys given to 2,566 patients entering treatment for opioid addiction between July 2009 and March 2012, before and after the 2010 introduction of ADF OxyContin [169]. During the 21-month post-ADF period, endorsement of hydrocodone or oxycodone agents other than OxyContin as the preferred opioid changed little from before ADF introduction, but endorsement of high-potency fentanyl or hydromorphone as the preferred opioid rose from 20.1% to 32.3%. Of opioids used in the past 30 days to get high, OxyContin fell from 47.4% to 30%, while heroin nearly doubled. More detailed questioning of 103 abusing patients found unanimous preference for the old OxyContin formulation, and 66% of those preferring pre-ADF OxyContin switched to another opioid, most commonly heroin. This switch appeared to be causally linked. No evidence suggested that OxyContin abusers quit using opioids as the result of ADF introduction; instead, they shifted their drug of choice to other opioids, primarily heroin. The authors concluded that ADF OxyContin successfully reduced OxyContin abuse, but also led to increased abuse of replacement opioids [169].

Analysis of data from the National Poison Data System, which covers the reporting from all U.S. poison centers, indicated that, in the period after ADF OxyContin introduction, abuse exposures decreased 36% for ADF OxyContin, increased 20% for other single-entity oxycodone, and increased 42% for heroin. Accidental opioid exposures decreased 39% for ADF OxyContin, increased 21% for heroin, and remained unchanged for other single-entity oxycodone products. The authors conclude that opioid analgesic ADFs can reduce abuse of the specific opioid product but may also lead to switching to other accessible non-ADF opioids [170].

Thus, the introduction of ADF opioids has driven a movement away from prescription opioids and to heroin and has increased the illicit price of traditional non-ADF opioids as they are phased out of the supply chain. During this abandonment by abusers and addicts of the precisely measured amount of pure drug in prescription opioids for the illicit street market of drug dealers, needles, and kitchen table chemists, public health officials and law enforcement agencies are noting increases in heroin overdoses, crime, and other public health problems [171]. These unanticipated negative consequences provide a compelling reminder that societal problems of substance abuse and addiction are complex and multifaceted. Simplistic solutions seeking only to restrict drug supply have never succeeded in reducing drug demand.

INCREASINGLY RESTRICTED ACCESS TO THERAPIES FOR OPIOID ADDICTION

Restricted access to opioid analgesics is also negatively impacting patients attempting to access treatment for opioid addiction. The opioid analgesics methadone and buprenorphine comprise the backbone of outpatient multidisciplinary treatment of opioid addiction in the United States. A 2013 press release by the ASAM states that investigation into state Medicaid and private insurance coverage found increasing restrictions due to policy changes over coverage, daily dose, prior authorizations, and the requirement of previous failed treatment approaches. The end result of these imposed barriers to accessing opioid addiction medications is an increase in patient denial of services, which ASAM states is senseless and unethical considering the epidemic-level rates of opioid addiction and overdose deaths [172].

PATIENT TERMINATION

Several clinical practice guidelines for safe opioid prescribing explicitly endorse patient termination in the event of abnormal UDT results, aberrant drug-related behaviors, other violations of the patient-provider contract, or deterioration in the provider-patient relationship [97; 118]. This approach is controversial, and as stated by Ballantyne, "The surest way to hurt patients (and society) is to abandon them when they deviate from the constructive relationship envisaged by the treating practitioner, only to trail from physician to physician to obtain the drug they need, or worse still, seek illicit supplies" [173].

Clinician response to aberrant behaviors should involve an assessment of seriousness, underlying cause, likelihood of recurrence, and clinical context of the aberrant behavior [116]. Occasional episodes of non-serious violations can be managed by patient education and enhanced monitoring [174]. The basis of opioid analgesic termination should be consistent with those for any other medication class, where discontinuation is prompted when opioid therapy benefits are outweighed by harms. Reasons given for termination include [175]:

- Opioids are no longer effective.
- Opioids no longer stabilize the patient or improve function.
- Patient has lost control over his or her use of the opioid.
- Patient is diverting drugs.
- Patient is not able to stop using alcohol, benzodiazepines, or other CNS depressants.
- Adverse effects become unmanageable.

PATIENTS WITH CHRONIC PAIN AND SUBSTANCE USE DISORDER

Alcohol, street drugs, and prescription medications are used by patients with chronic pain for diverse reasons, including the self-medication of pain, insomnia, depression or anxiety, or intrusive trauma memories; as recreation with occasional use; as a compulsive act driven by addiction; and to avoid withdrawal symptoms [176]. Chronic pain and substance use disorder often coexist, and each condition is a risk factor for the other. Whenever possible, active substance abuse disorder in patients with chronic pain should be treated because of safety concerns and because active substance use disorder interferes with the therapeutic progress in the pain condition due to overlapping mechanisms. Active addiction augments pain stimuli processing and perception through alterations in the input, processing, and modulation of nociceptive stimuli, sympathetic activation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and opioid tolerance (in active opioid addiction). Persons with addiction have reduced pain tolerance and increased pain perception, the result of baseline perceptual pathway reorganization from the interactive effects of both conditions [20].

Some personality traits common in patients with addiction, such as external locus of control and catastrophization, are predictors of poor outcome in pain therapy. Intoxication and withdrawal activate the sympathetic nervous system to augment pain perception and increase muscle tension, irritability, and anxiety. The depletion of brain dopamine associated with withdrawal exacerbates discomfort in addicted patients. Many patients with addiction have lost their network of social support, another factor associated with poor pain therapy outcome [20].

In susceptible persons with chronic pain, use of opioid analgesics for pain relief can lead to a cyclical relationship between pain symptoms, opioid use, and drug effect that is driven by positive and negative reinforcement. The positive reinforcement from opioids comes from induction of a pleasurable state such as euphoria or relaxation, with negative reinforcement coming from elimination of an unpleasant state such as pain or distress. In some patients with chronic pain and biopsychosocial risk factors for addiction, the reinforcing effects they experience from opioids are sufficiently powerful to compel compulsive efforts to replicate the drug experience. Chronic pain adds a layer of complexity to the development and management of opioid addiction. The positive and negative effects of opioids become more elusive over time, and tolerance develops to the analgesic effect. Attempts to cut back or quit can induce opioid withdrawal or the unmasking of severe pain. The patient becomes increasingly preoccupied with obtaining and using opioid analgesics to alleviate his or her intense physical and emotional distress. This preoccupation can be severe, to the point of involving the entirety of motivational resources. Although patients with chronic pain and opioid use disorder represent a complex and challenging population, these chronic co-occurring conditions can be effectively managed [175].

Some people have achieved durable recovery from their substance use disorder and also require medical care for long-standing pain or pain that developed and became chronic during their recovery. Although the former drug of choice is the agent most likely to lead to cravings and relapse, those with a history of addiction to any drug (or alcohol) are susceptible to developing an opioid use disorder in the context of pain treatment. It is important to note that among patients in recovery from a substance abuse disorder, risk of developing problematic opioid analgesic use is inversely proportional to their duration of recovery. While many patients with a previously active substance use disorder are forthcoming during the comprehensive assessment,

some may not be; others may lack an appreciation of either the gravity of their former substance abuse disorder or the clinical importance in disclosing this history to their healthcare provider. Family members can be a valuable resource in providing this information [175].

It is important for the prescriber to determine the recovery status of the patient in order to appropriately tailor the treatment plan. For patients who have achieved stable remission, corroborate and support them in their recovery. If a patient is receiving buprenorphine or methadone maintenance therapy for an opioid use disorder, verify and continue buprenorphine or methadone. If a patient has an active substance abuse disorder, refer him or her to a substance abuse specialist, if possible, for further evaluation [129; 175].

An important point is that clinicians often find patients with chronic pain to be difficult to treat, due to the pain condition often eluding diagnosis and the effects unrelenting pain can have on patient ability to interact calmly and civilly. A comorbid substance abuse disorder amplifies the likelihood of difficult behavior from the patient. Such patients can provoke strong negative responses from treatment providers, often based on either frustration from attempting to treat difficult or intractable problems or clinicians feeling they are working harder for the well-being of the patient than the patient is. It may be helpful for clinicians to remind themselves that, despite the apparent lack of patient motivation, no one would wish the experience of comorbid pain and addiction on anyone [175].

These patients have complex and intense needs, best served by a treatment team approach involving a team of professionals, including [177]:

- Primary care provider
- Addiction specialist
- Pain specialist
- Nurse
- Pharmacist
- Psychiatrist
- Psychologist
- Other behavioral health specialists, such as social workers or marriage and family therapists
- Physical or occupational therapists

To help build a therapeutic relationship with the patient, the following approach is suggested [175]:

- Listen actively.
- Ask open-ended, nonjudgmental questions.
- Restate patient accounts to make sure they have been understood.
- Use clarifying statements (e.g., "It sounds as if the pain is worse than usual this week").
- Demonstrate empathy. One approach is to acknowledge the effort required to simply get through each day with constant pain.
- Use feeling statements (e.g., "This must be very difficult for you").

Referral to an addiction professional for further substance abuse disorder evaluation and possible treatment does not negate patient need for pain treatment, because addiction treatment programs rarely have the resources or expertise to treat pain. Patients who are seeking treatment for chronic pain with an unacknowledged substance abuse disorder may react negatively when told of their referral to an addiction professional. The clinician-patient relationship is especially critical for patients who have comorbid pain and substance abuse disorders. They may anticipate clinician criticism or judgment of their substance use, dismissal of their pain complaints, or misinterpret concern over a possible substance abuse disorder as lack of concern for their pain. They may blame themselves for the substance abuse problem and expect their healthcare provider to respond in kind. Clinicians should convey respect and concern and reassure patients they fully understand the pain and the substance

abuse disorder are uninvited chronic illnesses requiring concurrent treatment. It is important to clearly explain the purpose of the referral, with the following approach suggested [175]:

- Present the substance abuse disorder referral as you would to any other specialist, using a matter-of-fact and unapologetic tone.
- Emphasize the importance of assessing all factors, including substance abuse disorders, that may be contributing to chronic pain and that ongoing problems with substance abuse can interfere with optimal treatment of chronic pain.
- Avoid focusing on patient explanations of their substance use.
- Reassure patients that further evaluation and possible treatment of their substance abuse problem does not mean abandonment by their healthcare provider or neglect of their chronic pain condition. Emphasize that their care will be coordinated among all involved professionals.
- Reassure the patient that federal regulations hold clinicians to a high standard of confidentiality concerning patient drug and alcohol treatment information.

TREATMENT OF SUBSTANCE USE DISORDER

Not infrequently, primary care providers do not have access to specialized addiction professionals or programs for patient referral. Although coexisting pain and addiction rank among the most challenging conditions to manage in primary care, recovery is possible. Providers should practice patience, flexibility, and consistent motivational support with the patient. When addiction specialists are lacking, clinicians should [176]:

- Identify contributory factors to the chronic pain and use of substances
- Encourage and support the patient in developing a self-care program
- Implement or refer to initiate active treatment of the various underlying factors
- Provide regular patient follow-up to monitor self-care and treatments and to revise the plan, as needed

The goals of treatment include avoiding harmful use of substances and achieving physical, psychological, and spiritual well-being. In patients with chronic pain with substance abuse disorders, there is a degree of overlap when substance abuse disorder treatment involves a biopsychosocial approach, as it ideally does. Effective approaches for substance abuse disorder include a combination of [176]:

- Cognitive-behavioral therapy that addresses addiction recovery and chronic pain
- Deep relaxation/meditation through mindfulness, progressive muscle relaxation, and/or other approaches
- Working with an addiction counselor to explore substance use issues and to support recovery
- 12-step program involvement, through Alcoholics Anonymous (AA), Narcotics Anonymous (NA), or Methadone Anonymous (MA), when appropriate. Every 12-step program has sponsors who are support persons successful in their recovery through their respective 12-step program, with a desire to work with new members to help them achieve recovery success. The patient should be encouraged to find a sponsor.
- Alternatives to 12-step programs for peer support in substance abuse recovery (e.g., Smart Recovery and Rational Recovery)
- Chronic Pain Anonymous, the peer-support program for those with chronic pain

Treatment of Opioid Use Disorder in Patients with Chronic Pain

For patients on chronic opioid therapy who have minor opioid abuse relapses but quickly regain stability, involving substance abuse counseling in the medical setting or through a formal addiction program may suffice. One problem is that many addiction treatment programs will not admit patients who require the ongoing use of opioid analgesics for pain. In patients whose frequent relapses indicate a serious opioid use disorder, the best option may be referral to an opioid treatment program for methadone therapy or initiation of buprenorphine [175]. Methadone and buprenorphine can be used in patients with opioid use disorder during detoxification. With this approach, the patient is slowly transitioned from the dose of their illicit opioid to an opioid-free state by switching the illicit opioid to the withdrawal medication and slowly decreasing the detoxification medication dose. However, in the context of treating the opioid use disorder, the patient is placed on methadone or buprenorphine for an extended period. Formerly termed "maintenance therapy," this is now called "medication-assisted treatment" [178].

Treatment of opioid addiction with methadone or buprenorphine is intended to stabilize dysregulated brain pathways, thereby reducing craving and relapse risk. Persons with opioid addiction remain at very high risk of opioid relapse after successful detoxification and cessation of acute opioid withdrawal symptoms. Profound changes in brain function that occur with the development and progression of opioid addiction become unmasked with cessation of opioid use. Factors contributing to relapse vulnerability in persons attempting recovery from opioid addiction include craving for opioids, hypersensitivity to emotional stress, an inability to experience pleasure or reward, and a persistent state of distress, anxiety, or malaise [179]. For many patients with opioid addiction, treatment should address these alterations in neurobiology. By targeting the same brain receptors and pathways as the abused opioid, pharmacotherapy with opioid agonists or partial agonists can effectively manage opioid withdrawal symptoms and play an essential part in the ongoing treatment plan [180]. Methadone and buprenorphine are the two most widely used and effective pharmacotherapies for opioid use disorder, and both have regulatory approval in the United States for this indication [181]. Naltrexone is also approved for treatment of opioid use disorder [100; 180]. In 2018, the FDA approved the first non-opioid for the management of opioid withdrawal symptoms [182]. Lofexidine may be used for up to 14 days to lessen the severity of symptoms of opioid withdrawal as part of a long-term treatment plan [100].

Methadone Therapy

Methadone has been in clinical use since 1965 as a treatment for opioid addiction. Its use is based on the principle that a long-acting mu opioid agonist at a sufficient dose prevents opioid withdrawal, blocks the desired effects if other opioid drugs are abused, and diminishes the craving for opioids [183]. A network of opioid treatment program regulatory and dispensing systems has been implemented to dispense methadone for opioid addiction, where the patient is administered methadone once a day under staff observation. Some stabilized patients are allowed up to a 30-day supply of take-home methadone, depending on their length of maintenance and compliance with other opioid treatment program rules. However, for some opioid-dependent persons, this system is not feasible due to lack of proximity to an opioid treatment program, a schedule that conflicts with that of an opioid treatment program, or concerns related to the social stigma associated with methadone [184].

Although the appropriate maintenance dose should be tailored to the individual on the basis of genetics and opioid use history, daily doses of 80–120 mg are common and are more likely to produce the desired opioid-blockade effect. Data indicate a greater reduction in illicit opioid use from a daily dose of 80–100 mg than from a dose of 40–60 mg [181; 184].

A potential issue with methadone relates to its metabolism by the hepatic cytochrome P450 CYP3A4 enzyme and the numerous medications that may adversely interact with its metabolism to result in elevation of plasma methadone level or rapid elimination of the drug. This can lead to dangerous toxicity or lack of effectiveness, respectively [100; 181].

Buprenorphine Therapy

Buprenorphine was the first drug approved for treatment of opioid addiction that can be prescribed in an office-based setting [185]. For use in opioid addiction therapy, buprenorphine is formulated into a product combined with the opioid antagonist naloxone and administered sublingually. When taken as prescribed, the naloxone component remains inert, but if the formulation is crushed and injected, the naloxone is activated to produce withdrawal symptoms. Buprenorphine occupies 85% to 92% of brain mu opioid receptors at 16 mg/day dosing and 94% to 98% at 32 mg/day. Daily doses of 4–16 mg are typically effective for most patients, with 16–24 mg the upper limit of recommended dosing [100; 186; 187]. Buprenorphine may be prescribed by clinicians with appropriate training and a Drug Addiction Treatment Act (DATA 2000) waiver [184; 188].

Several pharmacologic aspects of buprenorphine contribute to its safety and effectiveness as therapy for opioid addiction and make it highly suitable for use in primary care [189]. As a partial mu agonist, a ceiling effect exists for its maximal activity—beyond a certain dose, no additional benefit is experienced. In contrast to increases in the dose of pure opioid agonists such as methadone, a greater margin of safety exists from death by respiratory depression. Buprenorphine possesses a short plasma half-life (about four to six hours) and a long duration of action resulting from its high affinity for and slow dissociation from the mu opioid receptor [185]. This slow dissociation likely contributes to a reduction in the severity of withdrawal symptoms during detoxification, and the longer duration of action allows for the potential of alternate-day dosing [190].

Methadone and Buprenorphine Efficacy

The efficacy literature indicates that higher-dose methadone (>50 mg daily, and 60–100 mg per day in particular) is more effective than lower doses in reducing illicit opioid and possibly cocaine use [191]. Higher-dose methadone is comparable to higher-dose buprenorphine (≥8 mg daily) on measures of treatment retention and reduction of illicit opioid use [191]. Although 30–60 mg per day of methadone may be effective in resolving opioid withdrawal symptoms, some patients require a maintenance dose ≥120 mg per day to eliminate illicit opioid use [191]. Patients requiring high-dose methadone for more severe opioid addiction are unlikely to achieve the same benefit from higher-dose buprenorphine [121]. Methadone has been reported to have higher retention rates, whereas buprenorphine has a lower risk of overdose fatality. These risks should be appropriately weighed by the treating or referring physician [189].

Sustained stabilization on methadone or buprenorphine can greatly enhance the capacity for normal functioning, including holding a job, avoiding crime, and reducing exposure to infectious disease from injection drug use or risky sexual behavior. Stabilized patients are much more likely to benefit from counseling and group therapy, essential components of recovery [183]. Although patients may experience sedation during the induction phase, tolerance to this effect develops over several weeks, after which the ability to work safely or operate a car or machinery is no longer impaired. Cognitive research has found that, during stabilization, the methadone-maintained patient is just as capable as a healthy, non-addicted person in job performance, assuming education and skill is comparable and abstinence from opioids and other drugs of abuse is ongoing [192]. Unfortunately, serious stigma surrounds methadone treatment, experienced most acutely by patients but also by professionals, which may pose a barrier to treatment support [193].

While methadone and buprenorphine can effectively treat pathologic opioid use, they do not appear to significantly reduce non-opioid substance abuse. Both medications are approved for use as part of a broader, comprehensive, recovery-oriented medical and social support plan. Importantly, these medications are compatible with a recovery-oriented treatment approach, which research suggests can be an essential—but not sufficient—element of recovery from opioid addiction [194]. While methadone and buprenorphine can provide the patient with stabilization by suppressing withdrawal symptoms, craving, and dysphoria, many patients also experience mental health problems, deterioration in personal and social relationships, and greatly impaired occupational functioning. The addition of counseling, social services, monitoring, and peer supports can offer much of what pharmacotherapy cannot provide [184].

The effectiveness of methadone and buprenorphine has only been shown in their use as long-term maintenance, and there is little evidence to support their use as a short-term therapy course. This has been a source of patient and provider frustration. In clinicians, this probably reflects the antiquated perception that withdrawal and craving are the cardinal manifestations of addiction that, if properly treated for a brief period, should lead to full remission. It is now known that no short-term treatment can reverse the typically decades-long opioid-induced genetic expression, neurobiologically based cue-induced craving and withdrawal, or alteration in brain reward, motivation, and memory circuits characterizing long-term opioid addiction. There is increasingly widespread awareness that addiction should be viewed as a chronic disease, with great similarity to other chronic disease, such as diabetes and hypertension, whereby remission is dependent on medical management, lifestyle changes, and significant social supports [184].

Considerations in Addressing Chronic Pain

Although methadone and buprenorphine are highly effective in the treatment of some chronic pain conditions, the protocol by which they are administered to treat opioid use disorder is unlikely to provide sufficient analgesia for patients with chronic pain. With methadone, the 4- to 8-hour duration of analgesic action is significantly shorter than the 24- to 48-hour duration it suppresses opioid withdrawal and craving. The typical once-daily dosing results in a narrow window of analgesia, and contrary to popular belief, it is usually not adequate for analgesia in patients with chronic pain. Additional therapies are required. With patients often describing a six- to eight-hour window of analgesia from their usual morning dose, a single long-acting opioid dose in the afternoon or early evening may be sufficient for pain control for the remainder of the day [195].

With buprenorphine therapy, concurrent opioid analgesic use is complicated by buprenorphine pharmacodynamics. With high mu opioid receptor affinity, buprenorphine displaces or competes with full opioid agonists given concurrently. This can result in several types of adverse outcomes [15]:

- Inadequate analgesia from blocking the effect of concurrent opioids
- Opioid overdose when buprenorphine plasma level declines in the presence of high-dose concurrent opioids
- Acute opioid withdrawal syndrome as the buprenorphine plasma level declines in the presence of inadequate additional opioids
- Acute opioid withdrawal syndrome when buprenorphine is administered to patients receiving long-term opioid analgesic therapy

Buprenorphine has an analgesic duration of 4 to 8 hours and a 24- to 48-hour suppression of opioid withdrawal and craving. As a partial agonist, the analgesic effect has a ceiling after which dose escalation does not lead to improved pain control.

Thus, patients receiving buprenorphine for opioid use disorder must discontinue this medication if they require full-agonist opioid analgesics for chronic pain control. Before taking this step, the clinician and patient should weigh the risks and benefits, including the risks of prescription opioid abuse and potential relapse to drug use without buprenorphine, and the potential improvements in pain and function that may come with full-agonist opioid analgesic therapy [20].

Patients in recovery from opioid or other substance use disorders may have specific preferences for types of analgesic medications and may have greater awareness of their risk of relapse if given opioids for their chronic pain. Studies of patients with pain in recovery from substance use disorders have found that while some do relapse when receiving long-term opioid analgesic therapy, untreated pain can itself be a trigger for relapse. A prescription opioid agreement may help provide a sense of control that recovering addicts often fear losing when taking opioid analgesics [20].

CASE STUDY

An unemployed man, 64 years of age, is brought to an emergency department by ambulance, after his wife returned from work to find him lying on the couch, difficult to arouse and incoherent. He has a past history of hypertension, diabetes (non-insulin dependent), mild chronic obstructive pulmonary disease, and chronic back and shoulder pain, for which he has been prescribed hydrocodone/acetaminophen for many years. His wife reports that while he seemed his usual self when she left for work that morning, he had, in recent weeks, been more withdrawn socially, less active, and complained of greater discomfort from the back and shoulder pain. She knows little about his actual medication usage and expresses concern that he may have been taking more than the prescribed amount of "pain medicine."

On evaluation, the patient is somnolent and arouses to stimulation but is non-communicative and unable to follow commands. His blood pressure is normal, he is afebrile, and there are no focal neurologic deficits. Oxygen saturation, serum glucose, and routine laboratory studies (blood counts and metabolic profile) are normal except for mild elevation in blood urea nitrogen (BUN) and creatinine; the urine drug screen is negative except for opioids. Additional history from the family indicates that the patient has been admitted to other hospitals twice in the past three years with a similar presentation and recovered rapidly each time "without anything being found."

Following admission, the patient remains stable-to-improved over the next 12 to 18 hours. By the following day, he is awake and conversant and looks comfortable. On direct questioning, he reports recent symptoms of depression but no suicidal ideation. The patient describes an increased preoccupation with his pain syndrome, difficulty sleeping at night, and little physical activity during the day, in part because of physical discomfort. He is vague about his medication regimen and admits to taking "occasional" extra doses of hydrocodone for pain relief.

The family is instructed to bring in all his pill bottles from home, which they do. In addition to the hydrocodone prescribed by his primary care physician, there is a recent refill of a prescription for the medication given to the patient at the time of his last hospital discharge six months earlier.

ASSESSMENT

A full evaluation, including radiographic studies and consultation with psychiatry and physical therapy, is completed. The working diagnosis for the patient's acute illness is toxic encephalopathy caused by the sedative side effects of opioid medication on the CNS. It is explained that the combination of his advancing age and diabetes likely reduced the efficiency of his kidneys in clearing the medication and its metabolites, making him more susceptible to CNS sedation. It is noted that the

patient and his wife have little understanding of the rationale, proper use and safeguards, potential side effects, and limited effectiveness of opioid use for chronic pain.

In addition, the patient is diagnosed with poorly controlled chronic pain syndrome secondary to osteoarthritis and degenerative disc disease; exacerbating factors include deconditioning and reactive depression. The use of an opioid analgesic, at least for the near term, is considered appropriate, if dosed properly, monitored closely, and integrated into a comprehensive, multidisciplinary plan that includes treatment of depression and the use of adjunctive, nonpharmacologic modalities of care. In the setting of possible early diabetic nephropathy, the option of utilizing an NSAID, except for very brief periods of breakthrough pain, is not considered to be a safe option.

At discharge, and in consultation with his primary care physician, a written treatment and management plan addressing all aspects of the patient's care is presented to the patient and his wife for discussion and consent. Among the key issues addressed are:

- Goals: Improvement in subjective pain experience; improved function of daily living manifested by regular walking exercise and improved social interaction with family and friends; relief of depression; and in the long-term, anticipated withdrawal of opioid medication and resumption of part-time work and/or volunteer community activity
- Outpatient physical therapy and back exercise program to increase core muscular strength, improve flexibility, reduce pain, and increase exercise tolerance
- Patient and family counseling regarding the safe use, dosage regulation, side effects, and proper disposal of opioid medication
- Joint patient-physician responsibilities as regards to regular follow-up, monitoring of goals and treatment effectiveness, avoidance of "doctor-shopping," and assent to a single provider for prescription medication

FOLLOW-UP

On follow-up six weeks after discharge, the patient is noticeably improved. He reports that he feels stronger and is sleeping better. His affect is brighter, and he is getting out more. He has maintained his physical therapy and exercise routine and is compliant with his medication. Though he still has pain, it is noticeably less and he is coping better. He and his wife are encouraged by his progress, particularly in regard to his improved functional status.

CONCLUSION

Opioid analgesic medications can bring substantial relief to patients suffering from pain. However, the inappropriate use, abuse, and diversion of prescription drugs in America, particularly prescription opioids, has increased dramatically and has been identified as a national public health epidemic. A set of clinical tools, guidelines, and recommendations are now available for prescribers who treat patients with opioids. By implementing these tools, the clinician can effectively address issues related to the clinical management of opioid prescribing, opioid risk management, regulations surrounding the prescribing of opioids, and problematic opioid use by patients. In doing so, healthcare professionals are more likely to achieve a balance between the benefits and risks of opioid prescribing, optimize patient attainment of therapeutic goals, and avoid the risk to patient outcome, public health, and viability of their own practice imposed by deficits in knowledge.

APPENDIX: BIAS AND VALIDITY IN PAIN RESEARCH

In addition to training, experience, and clinical judgment, safe and effective treatment of pain is guided by developments in the area of pain medicine research. Clinician awareness of refinements, advances, and breakthroughs in the diagnosis and treatment of pain is most directly acquired from reading the published research. Conducting well-designed clinical research is challenging and complex. Obtaining accurate and relevant information to apply to patient care is often made more difficult by inadvertent bias and lack of reliable validity in the reporting of research findings. Outright data fraud is rare, but false claims and biased interpretation of results (often unintentional) are commonplace in publications of medical research in general and pain research specifically. In the area of pain treatment with opioid analgesics, major stakeholder influence over the reporting of dangers, risks, benefits, and effectiveness is pervasive [2; 97; 196; 197; 198].

Clinicians trying to make the most of their limited time by reading study abstracts may also be misinformed. A random selection of studies with abstracts from six widely read and influential medical journals (*JAMA*, *BMJ*, *Lancet*, *NEJM*, *Annals of Internal Medicine*, and the *Canadian Medical Association Journal*) found that 18% to 68% of abstracts reported information that was inconsistent with or absent from the body of the paper [199].

PUBLICATION BIAS

Publication bias occurs when trials showing statistically significant and positive results are disproportionately published, relative to trials with negative or inconclusive findings. This type of bias is common in published pharmacological research. Pharmaceutical industry research sponsorship is associated with significantly higher rates of pro-industry conclusions, publication constraints, and propensity to ignore the publication of negative findings [200; 201; 202; 203; 204; 205].

REPORTING BIAS

Reporting bias includes a diverse range of bias, misrepresentation, distortion, omission, exaggeration, or dismissal of data reported by the authors of a study or of data from other publications [206]. The effect, if not the intent, of reporting bias is to influence reader perception through a persuasive argument that favors the agenda, paradigm, or interest of the author, agency, or institution, or to diminish or discount a competing or opposing perspective. Reporting bias is just as widespread in pain research as it is in other areas of medicine, often appearing as concluding statements of safety or efficacy that are not supported by the actual evidence.

A medical issue or problem is considered "hot" when it becomes the focal point of publicity and intense investigation. Reports of research findings are less likely to be true in hotter areas of research. Prejudice can dominate a hot medical field to further undermine the validity of research findings. Highly prejudiced stakeholders can also create obstacles and obstruct efforts to publish information with opposing results [207].

Pressures of vested interests can lead to disappointing research outcomes being "spun" to present the findings in a more favorable light by creative use of data, statistics, and linguistics. Examples of linguistic spin include [208]:

- "Treatment X is expected to be a very mportant approach in the management of Disorder Y"
- "Treatment X effect size approached conventional statistical significance."

The use of "spin"—claiming treatment benefit without any supporting evidence from the data—is common, and safety claims with spin without supporting data also occur [209; 210; 211].

BIAS IN CLINICAL PRACTICE GUIDELINES

Concerns have sometimes been raised regarding bias in the development of clinical practice guidelines, involving the reviewed research, misrepresentation of the data, or failure to assess the quality of the evidence supporting the recommendations. Inadequate or weak evidence may lead to conclusions based on value judgments, organizational preferences, or opinion. Guidance is frequently misinterpreted as mandate, when individualized treatment is the best practice [212]. Clinical practice guideline authority and influence usually comes from the sponsoring organization and status of the publishing journal. Once issued, the organization may become the promoter and defender of the guidelines, and panel members the stakeholders in the acceptance of their recommendations [116; 213].

Bias can also negatively affect the validity of systematic reviews and meta-analyses that can form the basis of clinical practice guidelines. For example, several practice guidelines on long-term opioid therapy for chronic pain were published between 2008 and 2011. Although each guideline was based on analysis of essentially the same body of published research, the guideline conclusions differed markedly. The educated reader may look deeper for possible explanations for these discrepancies, including bias. Areas to explore would include the source of funding or sponsorship for development and financial and other material ties of the authors to industry, organization, or agency (e.g., slanted reporting of findings, conclusions consistent with industry of agency interests or agenda); the quality of evidence used to support a recommendation (by either endorsing or discouraging use of a drug, dose level, or therapy duration) and, in particular, weak evidence used inappropriately as definitive proof; whether the authors solely used published studies; and whether the studies used were industry funded [214].

FALLACIES OF ARGUMENT

Fallacies of evidence or argument are used in pain medicine research to support or defend a false conclusion (***Table 12***). Many are intended to convince the reader of a cause-effect relationship when the actual evidence is weak or absent. Considerable evidence is required to establish a true cause-effect relationship, and the evidence purported to show causation may actually reflect association instead. It is important to maintain a degree of critical thinking to avoid being persuaded into accepting a falsehood or rejecting a truth.

Cum Hoc, Ergo Propter Hoc Fallacy

A prototypical example of this type of fallacy comes from the 2011 CDC reporting of the same data in three publications related to a stated epidemic in opioid analgesic deaths and addiction and their direct relation to increasing opioid prescribing as reflected by sales data. Evidence to support this argument came from simultaneously increased trends in opioid analgesic sales, opioid analgesic overdose deaths, and addiction treatment admissions for opioid analgesics [210; 211; 217]. Many professionals found this persuasive evidence of a cause-effect relationship, and this conclusion was also reported by the news media and widely referenced in academic papers.

With causation inferred from correlational data, the fallacy in this reporting was that few alternate explanations for the correlations were presented. One credible explanation would have been exaggeration in the true rates of unintended overdose fatalities directly caused by opioid analgesics, a fact conceded by the CDC. Omitted entirely was discussion of the escalating population of patients with chronic pain. Sicker patients may also have been increasingly prescribed multiple medications with overdose potential for their disorders, including opioids.

ARGUMENTS USED TO SUPPORT ERRONEOUS CONCLUSIONS IN BIASED RESEARCH REPORTING		
Form of Argument	**Definition**	**Explanation or Example**
False conclusions of causation based on correlation		
Non causa pro causa (no cause for cause)	One or more events suggested as causing another event	Even when data show a statistically significant correlation, assumption of cause and effect is erroneous.
Cum hoc, ergo propter hoc (with this, therefore because of this)	Causation based on an association between two or more event trends or outcomes that occur together in time	1) The correlation may be significant, but correlation is not causation, and more research is needed to rule out other explanations for the association. 2) The direction of causation may be the reverse of the false conclusion.
Post hoc, ergo propter hoc (after this, therefore because of this)	Conclusion of causality based solely on the sequence of events	This is common in observational and open-label studies, because factors that actually influence outcome are not controlled for.
Regression fallacy	Pain severity declines over time to a lower average level during the natural course.	This "regression to the mean" can falsely be attributed to treatment effect.
Texas sharpshooter fallacy	Certain variables showing a close association are selected from a vast array of data, and a cause-effect relationship is concluded.	Common in data-mining studies and erroneous due to: 1) The data cluster may be the result of chance. 2) Even if not random, the cause may differ from what is stated by the researchers.
False arguments used in support of a conclusion		
Argumentum ad ignoratum (appeal to ignorance)	Missing evidence is itself evidence for lack of an effect.	Often seen in pain medicine, as when the lack of long-term controlled studies on opioid safety and efficacy in chronic pain is stated as evidence against long-term opioid use in chronic pain
Argumentum ad verecundiam (appeal to authority)	The high-status source of a publication is used to affirm the results.	In an argument with weak factual support, this is used to mislead the reader into not questioning the accuracy, reliability, or validity of the data the argument is based on.
Argumentum ad populum (appeal to the people or popularity)	The widespread use and acceptance of a practice prove its validity.	Argues that a popular treatment (e.g., homeopathic pain remedies) would not be so widely used if it did not work. Avoids the need to show credible evidence.
Illusory correlation	An expected relationship between data, observations, or events is found when a true causal relationship is absent.	This fallacy has been used when infrequent patient outcomes stand out and are generalized to represent all patient outcomes.

Table 12 continues on next page.

ARGUMENTS USED TO SUPPORT ERRONEOUS CONCLUSIONS IN BIASED RESEARCH REPORTING *(Continued)*		
False arguments used in support of a conclusion		
Reductionism	A large, complex phenomenon is oversimplified by reducing it to a smaller, simpler component.	Can occur when data from a small, highly select group of patients with pain, or even data of individual patients by anecdote, is used to characterize an entire population of patients.
The "no true Scotsman" fallacy	Used as an *ad hoc* rescue of a reductionist argument that comes under criticism	Reflected by statements such as "no true patient in pain would abuse their medication"
False dichotomy	Forces simple answers to complex questions with an argument in which only two choices are offered	Epidemiologic studies may record the rate of opioid abuse by the number persons who either did or did not ingest a non-prescribed opioid analgesic in the past year. This neglects any detailed analysis, such as motivation by untreated pain, inadequately treated pain, or desire to get high.
Myths of beneficence	Programs or policies are argued as beneficial to patients or the public and thus should be accepted.	This appeal to altruism and the presumption of good intentions may be used to deter examination of possibly deficient or biased reasoning or harmful unintended consequences.

Source: [215; 216] *Table 12*

Another reason that causal inference from correlational data is erroneous is that when causation is based on simultaneously occurring events, it is not possible to determine which event came first. The true direction of causation may actually be the reverse of that reported by researchers. For instance, studies finding a significant correlation between fibromyalgia and obesity in women concluded these female patients developed fibromyalgia because they were overweight. The order of events, such as whether obesity or fibromyalgia came first, was never examined, and it is just as likely the pain and disability associated with fibromyalgia promoted activity avoidance and weight gain or that medications used to treat fibromyalgia promoted weight gain or that medications used to treat fibromyalgia promoted weight gain.

False conclusions of a cause-effect relationship may also occur when data used in support of a conclusion come from small but statistically significant outcomes in a measure of effect, when broader examination of the data suggests otherwise. One example is the conclusion of a cause-effect relationship between higher methadone dose and frequency of the serious adverse cardiac event of QTc interval prolongation. The basis of this conclusion of causality was the finding of a modest yet statistically significant correlation between higher dose and adverse event [218; 219]. However, the conclusion is false because correlation does not equate with causality, and a closer look at the actual data revealed that increased QT interval occurred only in the subgroup who were abusing cocaine, a drug with well-known cardiotoxic effects.

Post Hoc Fallacy

An example of *post hoc* fallacy in reasoning comes from a prospective, observational, open-label study in which single-dose intrathecal midazolam was used in patients with failed back surgery syndrome. The patients showed significant pain reduction and few side effects, and the researchers concluded that single-dose intrathecal midazolam was an effective supplement to standard analgesic therapy [220].

This study was criticized for using a *post hoc*, *ergo propter hoc* argument as the basis for causation in a commentary published in the same journal issue [221]. The commentary noted that just because patients improved after midazolam treatment did not mean they improved because of midazolam treatment. From an evidence-based perspective, the study evidence would also be regarded as low quality because it lacked a control group and the open-label design did not control for placebo response.

Differences in Definitions

Differences in definitions also represent a serious confounding factor. Opioid "misuse" may describe overuse or underuse for medical purposes, non-medical use, or diversion, and may be a one-time occurrence or more frequent. There is little clarity or consistency across studies in how this variable is defined and measured. Consequently, the prevalence rate of opioid misuse can be expressed as a large or small probability depending on the study biases. This same phenomenon occurs with many other variables studied in pain management and can be very misleading to consumers of research.

Works Cited

1. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. *Exp Clin Psychopharmacol*. 2008;16(5):405-416.
2. Bruehl S, Apkarian AV, Ballantyne JC, et al. Personalized medicine and opioid analgesic prescribing for chronic pain: opportunities and challenges. *J Pain*. 2013;14(2):103-113.
3. Breuer B, Pappagallo M, Tai JY, Portenoy RK. U.S. board-certified pain physician practices: uniformity and census data of their locations. *J Pain*. 2007;8(3):244-250.
4. Schatman ME. The role of the health insurance industry in perpetuating suboptimal pain management. *Pain Med*. 2011;12(3): 415-426.
5. Schatman ME, Lebovits AH. On the transformation of the "profession" of pain medicine to the "business" of pain medicine: an introduction to a special series. *Pain Med*. 2011;12(3):403-405.
6. Webster LR, Cochella S, Dasgupta N, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. *Pain Medicine*. 2011;12(Suppl 2):S26-S35.
7. Institute of Medicine, Committee on Advancing Pain Research, Care, and Education. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: The National Academies Press; 2011.
8. Finch JW. Challenges of chronic pain management: public health consequences and considered responses. *N C Med J*. 2013;74(3):243-248.
9. American Academy of Family Physicians. AAFP Chronic Pain Management Toolkit. Available at https://www.aafp.org/patient-care/public-health/pain-opioids/cpm-toolkit.html. Last accessed August 5, 2020.
10. Federation of State Medical Boards. *Model Policy for the Use of Opioid Analgesics in the Treatment of Chronic Pain*. Washington, DC: Federation of State Medical Boards; 2013.
11. PRNewswire. U.S. Public and Doctors' Misperceptions Revealed in National Survey Demonstrate Urgent Need for Increased Opioid Dependence Awareness. Available at https://www.prnewswire.com/news-releases/us-public-and-doctors-misperceptions-revealed-in-national-survey-demonstrate-urgent-need-for-increased-opioid-dependence-awareness-210981471.html. Last accessed August 5, 2020.
12. Leavitt SB. Survey Shows Opioid "Addiction" Misunderstood. Available at https://neuropathyandhiv.blogspot.com/2013/07/understanding-opioid-addiction.html. Last accessed August 5, 2020.
13. Bhamb B, Brown D, Hariharan J, et al. Survey of select practice behaviors by primary care physicians on the use of opioids for chronic pain. *Curr Med Res Opin*. 2006;22(9):1859-1865.
14. Shipton EE, Bate F, Garrick R, Steketee C, Shipton EA, Visser EJ. Systematic review of pain medicine content, teaching, and assessment in medical school curricula internationally. *Pain Ther*. 2018;7(2):139-161.
15. Oliver J, Coggins C, Compton P, et al. American Society for Pain Management Nursing position statement: pain management in patients with substance use disorders. *Pain Manage Nurs*. 2012;13(3):169-183.
16. American Psychiatric Association. DSM-5 Fact Sheets: Changes in the New Edition. Available at https://www.psychiatry.org/psychiatrists/practice/dsm/educational-resources/dsm-5-fact-sheets. Last accessed August 5, 2020.
17. American Society of Addiction Medicine. Definition of Addiction. Available at https://www.asam.org/Quality-Science/definition-of-addiction. Last accessed August 5, 2020.
18. American Society of Addiction Medicine. Quality and Science. A Description of Addiction. Available at https://www.asam.org/Quality-Science/resource-links/a-description-of-addiction. Last accessed August 5, 2020.
19. Wallace LS, Keenum AJ, AbdurRaqeeb O, et al. Terminology matters: patient understanding of "opioids" and "narcotics." *Pain Pract*. 2013;13(2):104-108.
20. Prince V. Pain management in patients with substance-use disorders. In: *Chronic Illnesses I, II, and II I — PSAP-VII, Book 5*. Lenexa, KS: American College of Clinical Pharmacology; 2011.
21. Utah Department of Health. *Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain*. Salt Lake City, UT: Utah Department of Health; 2009.
22. American Academy of Family Physicians. AAFP Chronic Pain Resources. Available at https://www.aafp.org/dam/AAFP/documents/patient_care/pain_management/cpm-toolkit.pdf. Last accessed August 5, 2020.
23. Chou R, Fanciullo GJ, Fine PG, et al. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors—a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain*. 2009;10(2):131-146.
24. Passik SD, Kirsh SL, Whitcomb L, Dickerson PK, Theobald DE. Pain clinicians' rankings of aberrant drug-taking behaviors. *J Pain Palliative Care Pharmacother*. 2002;16(4):39-49.
25. Baxter J. Minimizing the Misuse of Prescription Opioids in Patients with Chronic Nonmalignant Pain. Available at https://www.drugabuse.gov/nidamed-medical-health-professionals/health-professions-education/centers-excellence/minimizing-misuse-prescription-opioids-in-patients-chronic-nonmalignant-pain. Last accessed August 5, 2020.

26. Passik SD. Issues in long-term opioid therapy: unmet needs, risks, and solutions. *Mayo Clin Proc*. 2009;84(7):593-601.
27. Holliday S, Hayes C, Dunlop A. Opioid use in chronic noncancer pain. Part 2: prescribing issues and alternatives. *Aust Fam Physician*. 2013;42(3):104-111.
28. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the opioid risk tool. *Pain Med*. 2005;6(6):432-442.
29. Hill CS. Government regulatory influences on opioid prescribing and their impact on the treatment of pain of non-malignant origin. *J Pain Symptom Manage*. 1996;11(5):287-298.
30. Joranson DE, Cleeland CS, Weissman DE, et al. Opioids for chronic cancer and noncancer pain: survey of state medical board members. *Fed Bull J Med Licensure Discipline*. 1992;79;15-49.
31. Catan T, Perez E. A Pain-Drug Champion Has Second Thoughts. Available at https://www.wsj.com/articles/SB10001424127887324478304578173342657044604. Last accessed August 5, 2020.
32. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain*. 1986;25:171-186.
33. Portenoy RK. Chronic opioid therapy for nonmalignant pain: from models to practice. *APS J*. 1992;1:285-288.
34. Portenoy RK. Chronic opioid therapy in nonmalignant pain. *J Pain Symptom Manage*. 1990;5:46-62.
35. Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. *J Pain Symptom Manage*. 1996;11: 203-217.
36. Portenoy RK. Opioid therapy for chronic nonmalignant pain: clinician's perspective. *J Law Med Ethics*. 1996;24:296-309.
37. Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med*. 1980;302:123.
38. Perry S, Heidrich G. Management of pain during debridement: a survey of U.S. burn units. *Pain*. 1982;13:267-280.
39. Medina JL, Diamond S. Drug dependency in patients with chronic headache. *Headache*. 1977;17:12-14.
40. Melzack R. The tragedy of needless pain. *Sci Am*. 1990;262:27-33.
41. American Academy of Pain Medicine, American Pain Society. The use of opioids for the treatment of chronic pain: a consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clin J Pain*. 1997;13(1):6-8.
42. Gussow L. Toxicology rounds: the dark truth behind pain as the fifth vital sign. *EMN*. 2013;35(3):4-5.
43. Compton WM. Prescription Drug Abuse: It's Not What the Doctor Ordered. Available at https://www.apa.org/about/gr/science/spin/2013/05/prescription-drug-abuse.pdf. Last accessed August 5, 2020.
44. U.S. General Accounting Office. Report to Congressional Requesters: Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem. Available at https://www.gao.gov/new.items/d04110.pdf. Last accessed August 5, 2020.
45. Baker DW. *The Joint Commission's Pain Standards: Origins and Evolution*. Oakbrook Terrace, IL: The Joint Commission; 2017.
46. The Joint Commission. Pain Management Standards for Accredited Organizations. Available at https://www.jointcommission.org/resources/patient-safety-topics/pain-management-standards-for-accredited-organizations/. Last accessed August 5, 2020.
47. R3 Report: Requirement, Rationale, Reference. Available at https://www.jointcommission.org/-/media/tjc/documents/standards/r3-reports/r3_report_issue_11_2_11_19_rev.pdf. Last accessed August 5, 2020.
48. Owen GT, Burton AW, Schade CM, Passik S. Urine drug testing: current recommendations and best practices. *Pain Physician*. 2012;15(3 Suppl):ES119-ES133.
49. Meier B. The Delicate Balance of Pain and Addiction. Available at https://www.nytimes.com/2003/11/25/science/the-delicate-balance-of-pain-and-addiction.html. Last accessed August 5, 2020.
50. Van Rooyan KW, Gelfand SG, Van Zee A, et al. A message from advocates for prescription opioid drug reform. *Pain Physician*. 2008;11:S63-S88.
51. U.S. Department of Justice. Drug Enforcement Administration. Diversion Control Division. ARCOS Retail Drug Summary Reports: Reporting Period – 2010. Available at https://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/2010/index.html. Last accessed August 5, 2020.
52. Centers for Disease Control and Prevention. Opioid Overdose: Prescribing Practices. Available at https://www.cdc.gov/drugoverdose/data/prescribing/prescribing-practices.html. Last accessed August 5, 2020.
53. Center for Substance Abuse Treatment. OxyContin: Prescription drug abuse—2008 revision. Available at https://store.samhsa.gov/product/OxyContin-Prescription-Drug-Abuse-2008-Revision/sma08-4138. Last accessed July 28, 2020.
54. Van Zee A. The promotion and marketing of OxyContin: commercial triumph, public health tragedy. *Am J Public Health*. 2009;99(2):221-227.
55. Tough P. The Alchemy of OxyContin. Available at https://www.nytimes.com/2001/07/29/magazine/the-alchemy-of-oxycontin.html. Last accessed August 5, 2020.
56. Katz DA, Hays LR. Adolescent OxyContin abuse. *J Am Acad Child Adolesc Psychiatry*. 2004;43(2):231-234.
57. Jayawant SS, Balkrishnan R. The controversy surrounding OxyContin abuse: issues and solutions. *Ther Clin Risk Manag*. 2005;1(2):77-82.

58. Brushwood DB. Why is Our Government Pursuing a War on Doctors? Available at https://www.dailystrength.org/group/chronic-pain/discussion/why-is-our-government-pursuing-a-war-on-doctor-s. Last accessed August 5, 2020.
59. Whelan E, Asbridge M, Haydt S. Representations of OxyContin in North American newspapers and medical journals. *Pain Res Manage*. 2011;16(4):252-258.
60. Giordano J, Schatman ME, Höver G. Ethical insights to rapprochement in pain care: bringing stakeholders together in the best interest(s) of the patient. *Pain Physician*. 2009;12(4):E265-E275.
61. Grand View Research. Opioids Market Size, Share, and Trends Analysis Report by Product, by Application, by Region, and segment Forecasts, 2019–2026. Available at https://www.grandviewresearch.com/industry-analysis/opioids-market. Last accessed August 5, 2020.
62. International Narcotics Control Board. Narcotic Drugs: Estimated World Requirements for 2020: Statistics for 2018. Available at https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2019/Narcotic_Drugs_Technical_Publication_2019_web.pdf. Last accessed August 5, 2020.
63. Hernandez SH, Nelson LS. Prescription drug abuse: insight into the epidemic. *Clin Pharmacol Ther*. 2010;88:307-318.
64. FDA Briefing Document. Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee. Available at https://www.fda.gov/media/134150/download. Last accessed August 5, 2020.
65. U.S. Department of Justice. Drug Enforcement Administration. 2019 National Drug Threat Assessment. Available at https://www.dea.gov/sites/default/files/2020-01/2019-NDTA-final-01-14-2020_Low_Web-DIR-007-20_2019.pdf. Last accessed August 5, 2020.
66. Lembke A. Why doctors prescribe opioids to known opioid abusers. *N Engl J Med*. 2012;367:1580-1581.
67. Croft P, Blyth FM, van der Windt D. The global occurrence of chronic pain: an introduction. In: Croft P, Blyth FM, van der Windt D (eds). *Chronic Pain Epidemiology: From Aetiology to Public Health*. Oxford: Oxford University Press; 2010.
68. Harkness EF, Macfarlane GJ, Silman AJ, McBeth J. Is musculoskeletal pain more common now than 40 years ago? Two population-based cross-sectional studies. *Rheumatology (Oxford)*. 2005;44:890-895.
69. Freburger JK, Holmes GM, Agans RP, et al. The rising prevalence of chronic low back pain. *Arch Intern Med*. 2009;169:251-258.
70. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact chronic pain among adults – United States, 2016. *MMWR*. 2018;67(36):1001-1006.
71. Substance Abuse and Mental Health Services Administration. Emergency Department Data. Available at https://www.samhsa.gov/data/data-we-collect/dawn-drug-abuse-warning-network. Last accessed August 5, 2020.
72. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. *The DAWN Report: Highlights of the 2011 Drug Abuse Warning Network (DAWN) Findings on Drug-Related Emergency Department Visits*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.
73. Substance Abuse and Mental Health Services Administration. Drug Abuse Warning Network (DAWN). Available at https://www.samhsa.gov/data/data-we-collect/dawn-drug-abuse-warning-network. Last accessed August 5, 2020.
74. Substance Abuse and Mental Health Services Administration. Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health. Available at https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHNationalFindingsReport2018/NSDUHNationalFindingsReport2018.pdf. Last accessed August 5, 2020.
75. Shield KD, Jones W, Rehm J, Fischer B. Use and nonmedical use of prescription opioid analgesics in the general population of Canada and correlations with dispensing levels in 2009. *Pain Res Manag*. 2013;18(2):69-74.
76. McCabe SE, Boyd CJ, Cranford JA, Teter CJ. Motives for nonmedical use of prescription opioids among high school seniors in the United States. *Arch Pediatr Adolesc Med*. 2009;163(8):739-744.
77. McCabe SE, West BT, Teter CJ, Boyd CJ. Medical and nonmedical use of prescription opioids among high school seniors in the United States. *Arch Pediatr Adolesc Med*. 2012;166(9):797-802.
78. McCabe SE, West BT, Boyd CJ. Leftover prescription opioids and nonmedical use among high school seniors: a multi-cohort national study. *J Adolesc Health*. 2013;52(4):480-485.
79. Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*. 2007;129(3):235-255.
80. Fishbain DA, Cole B, Lewis J, et al. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain Med*. 2008;9(4):444-459.
81. Boscarino JA, Rukstalis MR, Hoffman SN, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-IV diagnostic criteria. *J Addict Dis*. 2011;30(3):185-194.
82. Ballantyne JC, Sullivan MD, Kolodny A. Opioid dependence vs. addiction: a distinction without a difference? *Arch Intern Med*. 2012;172(17):1342-1343.
83. Elander J, Lusher J, Bevan D, Telfer P. Pain management and symptoms of substance dependence among patients with sickle cell disease. *Soc Sci Med*. 2003;57(9):1683-1696.

84. Manchikanti L, Cash KA, Malla Y, et al. A prospective evaluation of psychotherapeutic and illicit drug use in patients presenting with chronic pain at the time of initial evaluation. *Pain Physician*. 2013;16(1):E1-E13.
85. Jilani SM, Frey MT, Pepin D, et al. Evaluation of state-mandated reporting of neonatal abstinence syndrome – six states, 2013-2017. *MMWR*. 2019;68(1):6-10.
86. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA*. 2008;300(22):2613-2620.
87. Centers for Disease Control and Prevention. Opioid Overdose. Drug Overdose Deaths. Available at https://www.cdc.gov/drugoverdose/data/statedeaths.html. Last accessed August 5, 2020.
88. Cortez M. Opioids Given to Almost 1 in 4 Medicaid Patients, Study Finds. Available at https://www.bloomberg.com/news/articles/2017-06-21/opioids-given-to-almost-1-in-4-medicaid-patients-study-finds. Last accessed August 5, 2020.
89. Centers for Disease Control and Prevention. Overdose deaths involving prescription opioids among Medicaid enrollees—Washington, 2004–2007. *MMWR*. 2009;58(42);1171-1175.
90. Seattle Times Staff. Seattle Times Methadone Investigation Wins Pulitzer Prize. Available at https://www.seattletimes.com/seattle-news/seattle-times-methadone-investigation-wins-pulitzer-prize/. Last accessed August 5, 2020.
91. Berens MJ, Armstrong K. State Pushes Prescription Painkiller Methadone, Saving Millions but Costing Lives. Available at https://www.seattletimes.com/seattle-news/times-watchdog/state-pushes-prescription-painkiller-methadone-saving-millions-but-costing-lives/. Last accessed August 5, 2020.
92. Centers for Disease Control and Prevention. Vital Signs: overdoses of prescription opioid pain relievers and other drugs among women—United States, 1999–2010. *MMWR*. 2013;62(26):537-542.
93. Coplan P, Wentworth C, Downing J, et al. The risk of opioid overdose among patients receiving higher versus lower doses of extended-release opioids in the UK. *J Pain*. 2013;14(4 Suppl):S18.
94. Centers for Disease Control and Prevention. Vital Signs: risk for overdose from methadone used for pain relief—United States, 1999–2010. *MMWR*. 2012;61(26):493-497.
95. Madadi P, Hildebrandt D, Lauwers AE, Koren. Characteristics of opioid-users whose death was related to opioid-toxicity: a population-based study in Ontario, Canada. *PLoS ONE*. 2013;8(4):e60600.
96. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician*. 2008;11(2 Suppl):S63-S88.
97. Manchikanti L, Kaye AM, Knezevic NN, A et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. *Pain Physician*. 2017;20:S3-S92.
98. Boyles S. CDC: Alarming Increase in Methadone Deaths: Deaths from Opioid Painkillers have Tripled since 1999. Available at https://www.webmd.com/pain-management/news/20090930/alarming-increase-in-methadone-deaths#1. Last accessed August 5, 2020.
99. Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. *Pain Physician*. 2010;13(5):401-435.
100. Lexicomp Online. Available at https://online.lexi.com. Last accessed August 5, 2020.
101. The Joint Commission. Safe use of opioids in hospitals. *Sentinel Event Alert*. 2012;49:1-5.
102. The CBHSQ Report. Drug-Related Suicide Attempts by Middle-Aged Adults Likely to Involve Alcohol Combined with Drugs. Available at https://www.samhsa.gov/data/sites/default/files/report_2096/Spotlight-2096.pdf. Last accessed August 5, 2020.
103. Brauser D. ED Visits for Drug-Related Suicide Attempts Double. Available at https://www.medscape.com/viewarticle/829569. Last accessed August 5, 2020.
104. Hitchcock LS, Ferrell BR, McCaffery M. The experience of chronic nonmalignant pain. *J Pain Symptom Manage*. 1994;9:312-318.
105. Cheatle MD. Depression, chronic pain, and suicide by overdose: on the edge. *Pain Med*. 2011;12(Suppl 2):S43-S48.
106. Smith MT, Edwards RR, Robinson RC, Dworkin RH. Suicidal ideation, plans, and attempts in chronic pain patients: factors associated with increased risk. *Pain*. 2004;111(1-2):201-208.
107. Ratcliffe GE, Enns MW, Belik SL, Sareen J. Chronic pain conditions and suicidal ideation and suicide attempts: an epidemiologic perspective. *Clin J Pain*. 2008;24(3):204-210.
108. Tang NK, Crane C. Suicidality in chronic pain: a review of the prevalence, risk factors and psychological links. *Psychol Med*. 2006;36(5):575-586.
109. Torrance N, Elliott AM, Lee AJ, Smith BH. Severe chronic pain is associated with increased 10 year mortality: a cohort record linkage study. *Eur J Pain*. 2010;14(4):380-386.
110. Drew DJ, St. Marie BJ. Pain in critically ill patients with substance use disorder or long-term opioid use for chronic pain. *AACN Adv Crit Care*. 2011;22(3):238-254.
111. Apkarian AV, Sosa Y, Sonty S, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neuroscience*. 2004;24(46):10410-10415.

112. Golub A, Elliott L, Brownstein HH. The opiate pain reliever epidemic among U.S. arrestees, 2000–2010: regional and demographic variations. *J Ethn Subst Abuse*. 2013;12(1):1-29.
113. Fishman SM. *Responsible Opioid Prescribing: A Clinician's Guide*. 2nd ed. Washington, DC: Waterford Life Sciences; 2012.
114. Federation of State Medical Boards. *Guidelines for the Chronic Use of Opioid Analgesics*. Washington, DC: Federation of State Medical Boards; 2017.
115. U.S. Food and Drug Administration. Medication Guides: Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS). Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medication-guides-distribution-requirements-and-inclusion-risk-evaluation-and-mitigation-strategies. Last accessed August 5, 2020.
116. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113-130.
117. Gourlay DL, Heit HA. Universal precautions revisited: managing the inherited pain patient. *Pain Med*. 2009;10(Suppl 2):S115-S123.
118. Manchikanti L, Kaye AM, Knezevic NN, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. *Pain Physician*. 2017;20(2S):S3-S92.
119. Kaye AD, Jones MR, Kaye AM, et al. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: part 1. *Pain Phys*. 2017;20:S93-S109.
120. Butler SF, Budman SH, Fernandez KC, et al. Cross-validation of a screener to predict opioid misuse in chronic pain patients (SOAPP-R). *J Addict Med*. 2009;3(2):66-73.
121. Center for Substance Abuse Treatment. *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004.
122. Fine PG, Finnegan T, Portenoy RK. Protect your patients, protect your practice: practical risk assessment in the structuring of opioid therapy in chronic pain. *J Fam Pract*. 2010;59(9 Suppl 2):S1-S169.
123. Katz NP. *Opioid Prescribing Toolkit: A Workbook for Clinicians*. New York, NY: Oxford University Press; 2010.
124. Webster LR. Eight Principles for Safe Opioid Prescribing. Paper presented at: American Academy of Pain Medicine Annual Meeting; April 2013; Fort Lauderdale, FL.
125. American Chronic Pain Association. ACPA Resource Guide to Chronic Pain Treatment: 2018 Edition. Available at https://www.theacpa.org/wp-content/uploads/2018/03/ACPA_Resource_Guide_2018-Final-v2.pdf. Last accessed August 5, 2020.
126. American Pharmacists Association. VIGIL Helps Pharmacists Screen Controlled Substances. Available at https://www.pharmacist.com/vigil-helps-pharmacists-screen-controlled-substances. Last accessed August 5, 2020.
127. Strickland JM, Huskey A, Brushwood DB. Pharmacist-physician collaboration in pain management practice. *J Opioid Manag*. 2007;3(6):295-301.
128. Crespi-Lofton J. VIGIL: answer the question, "Is it legitimate?" *Pharm Today*. 2006;12(1):1.
129. Passik SD, Kirsh KL, Whitcomb L, et al. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. *Clin Ther*. 2004;26(4):552-561.
130. Atluri SL, Akbik H, Sudarshan G. Prevention of opioid abuse in chronic non-cancer pain: an algorithmic, evidence-based approach. *Pain Physician*. 2012;15(3 Suppl):ES177-ES189.
131. Meier B. Increase in Urine Testing Raises Ethical Questions. Available at https://www.nytimes.com/2013/08/02/business/increase-in-urine-testing-raises-ethical-questions.html. Last accessed August 5, 2020.
132. Sekhon R, Aminjavahery N, Davis CN Jr, et al. Compliance with opioid treatment guidelines for chronic noncancer pain (CNCP) in primary care at a Veterans Affairs Medical Center (VAMC). *Pain Med*. 2013;14(10):1548-1556.
133. American College of Preventive Medicine. Use, Abuse, Misuse and Disposal of Prescription Pain Medication Clinical Reference: A Resource from the American College of Preventive Medicine. Available at http://www.yuma.usmc-mccs.org/mccsyuma/assets/File/Drug%20Facts%20Sheets/painmedsclinicalreference.pdf. Last accessed August 5, 2020.
134. Office of National Drug Control Policy. Proper Disposal of Prescription Drugs. Available at https://www.ncjrs.gov/ondcppubs/publications/pdf/prescrip_disposal.pdf. Last accessed August 5, 2020.
135. U.S. Food and Drug Administration. Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release and Long-Acting Opioid Analgesics. Available at https://www.fda.gov/drugs/information-drug-class/opioid-analgesic-risk-evaluation-and-mitigation-strategy-rems. Last accessed August 5, 2020.
136. U.S. Food and Drug Administration. Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS). Available at https://www.fda.gov/media/82673/download. Last accessed August 5, 2020.
137. Webster L, St Marie B, McCarberg B, et al. Current status and evolving role of abuse-deterrent opioids in managing patients with chronic pain. *J Opioid Manag*. 2011;7(3):235-245.

138. Stanos SP, Bruckenthal P, Barkin RL. Strategies to reduce the tampering and subsequent abuse of long-acting opioids: potential risks and benefits of formulations with physical or pharmacologic deterrents to tampering. *Mayo Clin Proc*. 2012;87(7):683-694.

139. Green TC. Cumulative Impacts of ADFs/TRFs: Evidence from ASI-MV and the RARx Study. Paper presented at: 7th Annual RADARS Scientific Meeting; April 2013; Rockville, MD.

140. Budman SH, Grimes Serrano JM, Butler SF. Can abuse-deterrent formulations make a difference? Expectation and speculation. *Harm Reduct J*. 2009;29:6-8.

141. Passik SD, Hays L, Eisner N, Kirsh KL. Psychiatric and pain characteristics of prescription drug abusers entering drug rehabilitation. *J Pain Palliative Care Pharmacother*. 2006;20(2):5-13.

142. U.S. Food and Drug Administration. FDA Issues Draft Guidance on Abuse-Deterrent Opioids. Available at https://wayback.archive-it.org/7993/20161023125734/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm334785.htm. Last accessed August 5, 2020.

143. Butler SF, Cassidy TA, Chilcoat H, et al. Abuse rates and routes of administration of reformulated extended-release oxycodone: initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. *J Pain*. 2013;14(4):351-358.

144. Severtson SG, Bartelson BB, Davis JM, et al. Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010. *J Pain*. 2013;14(10):1122-1130.

145. Coplan PM, Kale H, Sandstrom L, Landau C, Chilcoat HD. Changes in oxycodone and heroin exposures in the National Poison Data System after introduction of extended-release oxycodone with abuse-deterrent characteristics. *Pharmacoepidemiol Drug Saf*. 2013;22(12):1274-1282.

146. Cicero TJ, Ellis MS. Abuse-deterrent formulations and the prescription opioid abuse epidemic in the United States: lessons learned from OxyContin. *JAMA Psychiatry*. 2015;72(5):424-430.

147. Behm A, Low KM, Medina M. Opioids with abuse-deterrent technologies: what role do they play in managing chronic pain in older adults? *Clin Geriatr*. 2012;20(7):26-32.

148. U.S. Food and Drug Administration. FDA Approves Abuse-Deterrent Labeling for Reformulated OxyContin: Agency Will Not Approve Generics to Original OxyContin. Available at https://wayback.archive-it.org/7993/20170112223041/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm348252.htm. Last accessed August 5, 2020.

149. Adams S. Painkiller Abuse Spurs Search for a Safer Opioid Therapy. Available at https://www.firstwordpharma.com/node/1115714?tsid=17. Last accessed August 5, 2020.

150. U.S. Food and Drug Administration. FDA Approves Extended-Release, Single-Entity Hydrocodone Product with Abuse-Deterrent Properties. Available at https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm420978.htm. Last accessed August 5, 2020.

151. U.S. Food and Drug Administration. FDA Requests Removal of Opana ER for Risks Related to Abuse. Available at https://www.fda.gov/news-events/press-announcements/fda-requests-removal-opana-er-risks-related-abuse. Last accessed August 5, 2020.

152. Magnani B, Kwong T. Urine drug testing for pain management. *Clin Lab Med*. 2012;32(3):379-390.

153. Reifler LM, Droz D, Bailey JE, et al. Do prescription monitoring programs impact state trends in opioid abuse/misuse? *Pain Med*. 2012;13(3):434-442.

154. Hannon K. The Prescription Drug Crisis in New York State: A Comprehensive Approach. Available at https://www.scribd.com/doc/82474334/Prescription-Drug-Abuse-Crisis-in-NYS-Comprehensive-Approach-New. Last accessed August 5, 2020.

155. Kraman P. Rx for Prescription Drug Abuse. Available at https://www.scribd.com/doc/82474334/Prescription-Drug-Abuse-Crisis-in-NYS-Comprehensive-Approach-New. Last accessed August 5, 2020.

156. Centers for Disease Control and Prevention. Opioid Overdose: State Prescription Drug Laws. Available at https://www.cdc.gov/drugoverdose/policy/laws.html. Last accessed August 5, 2020.

157. Meier B. FDA Urging a Tighter Rein on Painkillers. Available at https://www.scribd.com/doc/82474334/Prescription-Drug-Abuse-Crisis-in-NYS-Comprehensive-Approach-New. Last accessed August 5, 2020.

158. WorkCompWire. NCOIL Takes Lead on Best Practices to Curb Opioid Abuse. Available at https://www.workcompwire.com/2013/07/ncoil-takes-lead-on-best-practices-to-curb-opioid-abuse/. Last accessed August 5, 2020.

159. Department of Health and Human Services. Response to Citizen Petition Submitted by Physicians for Responsible Opioid Prescribing (PROP): Docket No. FDA-2012-P-0818. Available at https://www.supportprop.org/wp-content/uploads/2014/12/FDA_CDER_Response_to_Physicians_for_Responsible_Opioid_Prescribing_Partial_Petition_Approval_and_Denial.pdf. Last accessed August 5, 2020.

160. Ashby M, Fleming B, Wood M, et al. Plasma morphine and glucuronide (M3G and M6G) concentrations in hospice inpatients. *J Pain Symptom Manage*. 1997;14(3):157-167.

161. Schneider J, Anderson A, Tennant F. Patients who require ultra-high opioid doses. *Pract Pain Manag*. 2009;9(7):10-16.

162. Holmquist GL. Opioid metabolism and effects of cytochrome P450. *Pain Med*. 2009;10(Suppl 1):S20-S29.

163. Clarke T. U.S. War on Drugs Moves to Pharmacy from Jungle. Available at https://www.reuters.com/article/dea-prescription-drugs/feature-u-s-war-on-drugs-moves-to-pharmacy-from-jungle-idUSL1E8HC9GU20120616. Last accessed August 5, 2020.
164. Ryan H. Heroin Resurgence An 'Unintended Consequence' of Attempt to Curb OxyContin Abuse, Study Finds. Available at https://www.latimes.com/local/lanow/la-me-oxycontin-20170109-story.html. Last accessed August 5, 2020.
165. Alpert A, Powell D, Pacula RL. Supply-Side Drug Policy in the Presence of Substitutes: Evidence from the Introduction of Abuse-Deterrent Opioids. Available at https://www.nber.org/papers/w23031. Last accessed August 5, 2020.
166. Lipari RN, Hughes A. Trends in Heroin Use in the United States: 2002 to 2013. Available at https://www.samhsa.gov/data/sites/default/files/report_1943/ShortReport-1943.html. Last accessed August 5, 2020.
167. SAMHSA, Hughes A, Williams MR, Lipari RN, et al. National Survey on Drug Use and Health. NSDUH Data Review: Prescription Drug Use and Misuse in the United States: Results from the 2015 National Survey on Drug Use and Health. Available at https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR2-2015/NSDUH-FFR2-2015.pdf. Last accessed August 5, 2020.
168. National Institute on Drug Abuse. What is the Scope of Heroin Use in the United States. Available at https://www.drugabuse.gov/publications/research-reports/heroin/scope-heroin-use-in-united-states. Last accessed August 5, 2020.
169. Cicero TJ, Ellis MS, Surratt HL. Effect of abuse-deterrent formulation of OxyContin. *N Engl J Med*. 2012;367;187-189.
170. Coplan PM, Kale H, Sandstrom L, Landau C, Chilcoat HD. Changes in oxycodone and heroin exposures in the National Poison Data System after introduction of extended-release oxycodone with abuse-deterrent characteristics. *Pharmacoepidemiol Drug Saf*. 2013;22(12):1274-1282.
171. Ryan H, Glover S, Girion L. How Black-Market OxyContin Spurred a Town's Descent Into Crime, Addiction and Heartbreak. Available at https://www.latimes.com/projects/la-me-oxycontin-everett/. Last accessed August 5, 2020.
172. American Society of Addiction Medicine. Effective Rx Thwarted for Deadly Opioid Epidemic. Available at https://www.asam.org/docs/default-source/pressreleases/effective-rx-thwarted-for-deadly-opioid-epidemic-2013-06-20.pdf?sfvrsn=2. Last accessed August 5, 2020.
173. Ballantyne JC. Opioids for chronic nonterminal pain. *South Med J*. 2006;99(11):1245-1255.
174. Fleming MF, Balousek SL, Klessig CL, et al. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain*. 2007;8(7):573-582.
175. Substance Abuse and Mental Health Services Administration. *Managing Chronic Pain in Adults With or in Recovery from Substance Use Disorders*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2011.
176. Savage SR. What to do when pain and addiction coexist. *Chronic Pain Perspect*. 2013;62(6 Suppl):S10-S16.
177. Sanders SH, Harden RN, Vicente PJ. Evidence-based clinical practice guidelines for interdisciplinary rehabilitation of chronic nonmalignant pain syndrome patients. *Pain Pract*. 2005;5(4):303-315.
178. White WL. Medication-assisted recovery from opioid addiction: historical and contemporary perspectives. *J Addict Dis*. 2012;31(3):199-206.
179. Aston-Jones G, Harris GC. Brain substrates for increased drug seeking during protracted withdrawal. *Neuropharmacology*. 2004;47(Suppl 1):167-179.
180. Substance Abuse and Mental Health Services Administration. Medication-Assisted Treatment (MAT). Available at https://www.samhsa.gov/medication-assisted-treatment. Last accessed August 5, 2020.
181. Tetrault JM, Fiellin DA. Current and potential pharmacological treatment options for maintenance therapy in opioid-dependent individuals. *Drugs*. 2012;72(2):217-228.
182. U.S. Food and Drug Administration. FDA Approves the First Non-Opioid Treatment for Management of Opioid Withdrawal Symptoms in Adults. Available at https://www.fda.gov/news-events/press-announcements/fda-approves-first-non-opioid-treatment-management-opioid-withdrawal-symptoms-adults. Last accessed August 5, 2020.
183. National Institute on Drug Abuse. Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition). Available at https://www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition/preface. Last accessed August 5, 2020.
184. Treatment Research Institute. FDA approved medications for the treatment of opiate dependence: literature reviews on effectiveness and cost-effectiveness. In: *Advancing Access to Addiction Medications: Implications for Opioid Addiction Treatment*. Rockville, MD: American Society of Addiction Medicine; 2013: 13-15.
185. Center for Substance Abuse Treatment. *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs*. Rockville, MD: U.S. Department of Health and Human Services; 2005.
186. Colson J, Helm S, Silverman S. Office-based opioid dependence treatment. *Pain Physician*. 2012;15(3 Suppl):ES231-ES236.
187. Kampman, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. Available at https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-jam-article.pdf. Last accessed August 5, 2020.

188. Drug Enforcement Administration, Diversion Control Division. DATA Waived Physicians. Available at https://www.deadiversion.usdoj.gov/pubs/docs/index.html. Last accessed August 5, 2020.
189. Kahan M, Wilson L, Mailis-Gagnon A, Srivastava A; National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 2: special populations. *Can Fam Physician*. 2011;57(11):1269-1276, e419-e428.
190. Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. *Sci Pract Perspect*. 2002;1(1):13-20.
191. Van den Brink W, Haasen C. Evidence-based treatment of opioid-dependent patients. *Can J Psychiatry*. 2006;51(10):635-646.
192. Specka M, Finkbeiner T, Lodemann E, et al. Cognitive-motor performance of methadone-maintained patients. *Eur Addict Res*. 2000;6(1):8-19.
193. White W. *Long-Term Strategies to Reduce the Stigma Attached to Addiction, Treatment, and Recovery within the City of Philadelphia (with Particular Reference to Medication-Assisted Treatment/Recovery)*. Philadelphia, PA: Department of Behavioral Health and Mental Retardation Services; 2009.
194. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA*. 2000;284(13):1689-1695.
195. Olsen Y, Alford DP. Chronic pain management in patients with substance use disorders. *Adv Stud Med*. 2006;6(3):111-123.
196. Becker WC, Fraenkel L, Kerns RD, Fiellin DA. A research agenda for enhancing appropriate opioid prescribing in primary care. *J Gen Intern Med*. 2013;28(10):1364-1367.
197. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA*. 2016;315(15):1624-1645.
198. Macerollo AA, Mack DO, Oza R, Bennett IM, Wallace LS Academic family medicine physicians' confidence and comfort with opioid analgesic prescribing for patients with chronic nonmalignant pain. *J Opioid Manag*. 2014;10(4):255-261.
199. Pitkin RM, Branagan MA, Burmeister LF. Accuracy of data in abstracts of published research articles. *JAMA*. 1999;281(12):1110-1111.
200. Bekelman JE, Li Y, Gross CP: Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA*. 2003;289(4):454-465.
201. McGauran N, Wieseler B, Kreis J, Schüler YB, Kölsch H, Kaiser T. Reporting bias in medical research: a narrative review. *Trials*. 2010;11:37.
202. Ross JS, Mulvey GK, Hines EM, et al. Trial publication after registration in ClinicalTrials.gov: a cross-sectional analysis. *PLoS Med*. 2009;6(9):e1000144.
203. Mathieu S, Boutron I, Moher D, et al. Comparison of registered and published primary outcomes in randomized controlled trials. *JAMA*. 2009;302(9):977-984.
204. Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross-sectional study. *BMJ*. 2012;344:d7373.
205. Veitch E. Silent Takedown of the Pharma Trials Database…and More. Available at https://speakingofmedicine.plos.org/2012/03/23/silent-takedown-of-the-pharma-trials-databaseand-more/. Last accessed August 5, 2020.
206. Prasad V, Cifu A, Ioannidis JPA. Reversals of established medical practices: evidence to abandon ship. *JAMA*. 2012;307(1):37-38.
207. Ioannidis JPA. Why most published research findings are false. *PLoS Med*. 2005;8(2):696-701.
208. Chew M. Researchers, like politicians, use "spin" in presenting their results, conference hears. *BMJ*. 2009;339:b3779.
209. Yavchitz A, Boutron I, Bafeta A, et al. Misrepresentation of randomized controlled trials in press releases and news coverage: a cohort study. *PLoS Med*. 2012;9:e1001308.
210. Centers for Disease Control and Prevention. Vital Signs: Prescription Painkiller Overdoses in the U.S. Available at https://www.cdc.gov/vitalsigns/painkilleroverdoses/. Last accessed August 5, 2020.
211. Paulozzi LJ, Jones CM, Mack KA, Rudd RA. Vital Signs: overdoses of prescription opioid pain relievers—United States, 1999–2008. *MMWR*. 2011;60(43):1487-1492.
212. Shaneyfelt TM, Centor RM. Reassessment of clinical practice guidelines. *JAMA*. 2009;301(8):868-869.
213. Sniderman AD, Furberg CD. Why guideline-making requires reform. *JAMA*. 2009;301(4):429-431.
214. Pannucci CJ, Wilkins EG. Identifying and avoiding bias in research. *Plast Reconstr Surg*. 2010;126(2):619-625.
215. Mills JL. Data torturing. *N Engl J Med*. 1993;329(16):1196-1199.
216. Greenhalgh T. How to read a paper: statistics for the non-statistician. II: "significant" relations and their pitfalls. *BMJ*. 1997;315(7105):422-425.
217. Centers for Disease Control and Prevention. Policy Impact: Prescription Painkiller Overdoses. Available at https://www.cdc.gov/drugoverdose/pdf/policyimpact-prescriptionpainkillerod-a.pdf. Last accessed August 5, 2020.

218. Peles E, Bodner G, Kreek MJ, Rados V, Adelson M. Corrected-QT intervals as related to methadone dose and serum level in methadone maintenance treatment (MMT) patients: a cross-sectional study. *Addiction*. 2007;102(2):289-300.

219. Schmittner J, Krantz MJ. QTc prolongation in methadone maintenance: fact and fiction. *Heroin Addict Relat Clin Probl*. 2006;8(4):41-52.

220. Prochazka J, Hejcl A, Prochazkova L. Intrathecal midazolam as supplementary analgesia for chronic lumbar pain: 15 years' experience. *Pain Med*. 2011;12(9):1309-1315.

221. Bogduk N. When data are not proof. *Pain Med*. 2011;12(9):1297-1298.

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