PRESCRIPTION DRUG DIVERSION AND PAIN

History, Policy, and Treatment

Edited by

JOHN F. PEPPIN, JOHN J. COLEMAN, KELLY K. DINEEN, *and* ADAM J. RUGGLES

OXFORD

Prescription Drug Diversion and Pain

HISTORY, POLICY, AND TREATMENT

Edited by

John F. Peppin, DO, FACP
DIRECTOR
CENTER FOR BIOETHICS, PAIN MANAGEMENT AND MEDICINE
FLORHAM PARK, NEW JERSEY, NJ
CLINICAL ADJUNCT PROFESSOR
MARIAN UNIVERSITY, COLLEGE OF OSETOPATHIC MEDICINE
INDIANAPOLIS, IN
CONSULTANT
HAMDEN, CT

John J. Coleman, MA, MS, PhD
ASSISTANT ADMINISTRATOR (RETIRED)
DRUG ENFORCEMENT ADMINISTRATION
FOUNDER AND PRESIDENT (RETIRED)
PRESCRIPTION DRUG RESEARCH CENTER LLC
CLIFTON, VA

Kelly K. Dineen, RN, JD, PhD
ASSISTANT PROFESSOR OF LAW
DIRECTOR, HEALTH LAW PROGRAM
CREIGHTON UNIVERSITY SCHOOL OF LAW
OMAHA, NE

Adam J. Ruggles, JD, MA
ATTORNEY AND BIOETHICIST
EVANSVILLE, IN

OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS

Oxford University Press is a department of the University of Oxford. It furthers the University's objective of excellence in research, scholarship, and education by publishing worldwide. Oxford is a registered trade mark of Oxford University Press in the UK and certain other countries.

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America.

Library of Congress Cataloging-in-Publication Data
Names: Peppin, John F., editor. | Coleman, John J., Ph. D., editor. | Dineen, Kelly K., editor. | Ruggles, Adam J., editor.
Title: Prescription drug diversion and pain: history, policy, and treatment /
edited by John F. Peppin, John J. Coleman, Kelly K. Dineen, Adam J. Ruggles.
Description: New York, NY : Oxford University Press, [2018] | Includes bibliographical references.
Identifiers: LCCN 2018000838 | ISBN 9780199981830 (pbk.)
Subjects: | MESH: Analgesics, Opioid | Chronic Pain—therapy | Drug and Narcotic Control |
Prescription Drug Diversion—prevention & control | Opioid-Related Disorders—prevention & control | United States
Classification: LCC RC568.O45 | NLM QV 89 | DDC 615.7/822—dc23
LC record available at https://lccn.loc.gov/2018000838

9 8 7 6 5 4 3 2 1
Printed by WebCom, Inc., Canada

We dedicate this volume to the memory of two wonderful health professionals and human beings. This project has been plagued by sadness for most of the editors. Soon after starting this project, Dr. Howard Smith passed away suddenly. Howard was a wonderful man, dedicated to advancing the science and treatment of pain. He was gracious and was always willing to help others build their careers. He will be sorely missed. Dr. Kenneth L. Kirsh was a dear friend who spent his professional life trying to improve the lives of chronic pain patients. Soon after starting work on this volume, Ken was diagnosed with advanced cancer and was not able to continue with this project. He passed away in March 2017. He too was a wonderful person who will be missed by his friends, colleagues, family, and patients.

CONTENTS

CONTRIBUTORS

Timothy Atkinson, PharmD, BCPS, CPE
Clinical Pharmacy Specialist, Pain Management
Veterans Affairs Tennessee Valley Healthcare System
Murfreesboro, TN

Pravardhan Birthi, MD
Interventional Pain and PM&R Physician
CHI Health Saint Francis Pain and Physical Medicine Clinic
Grand Island, NE

Martin D. Cheatle, PhD
Associate Professor
Center for Studies of Addiction
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA

Yvonne D'Arcy, MS, ARNP-C, CNS, FAANP
Pain Management and Palliative Care Nurse Practitioner
Ponte Vedra, FL

Jeffrey Fudin, BS, PharmD, DAIPM FCCP, FASHP, FFSMB
Chief Executive Officer and Chief Medical Officer, Remitigate LLC
Delmar, NY
Clinical Pharmacy Specialist and Director, PGY2 Pharmacy Pain Residency (WOC)
Stratton VA Medical Center
Adjunct Associate Professor of Pharmacy Practice
Albany College of Pharmacy & Health Sciences
Albany, NY
Adjunct Assistant Professor of Pharmacy Practice
Western New England University College of Pharmacy
Springfield, MA

Kelly N. Gable, PharmD, BCPP
Associate Professor
Southern Illinois University Edwardsville School of Pharmacy
Edwardsville, IL

Christopher M. Herndon, PharmD, BCPS, CPE, FASHP
Associate Professor
Southern Illinois University Edwardsville
School of Pharmacy
Edwardsville, IL

Hani Raoul Khouzam, MD, MPH, FAPA
Staff Psychiatrist
Chief of Salinas Outpatient Adult Services
Natividad Medical Center
Salinas, CA

Bill H. McCarberg, MD, FABPM
Neighborhood Healthcare (FQHC)
Elizabeth Hospice
San Diego, CA

Michael E. Schatman, PhD
Department of Public Health and Community Medicine
Tufts University School of Medicine
Boston, MA

Anand C. Thakur, MD
CEO/Medical Director
ANA Pain Management
Clinical Assistant Professor
Department of Anesthesiology
Wayne State University
Detroit, MI

DISCLOSURES

Pravardhan Birthi, Martin D. Cheatle, John J. Coleman, Kelly N. Gable, Christopher M. Herndon, Hani Raoul Khouzam, Michael E. Schatman: Potential conflicts of interest.

Timothy Atkinson: Axial Healthcare Inc. (Consultant); Daichii Sankyo (Advisory Board); Purdue Pharma (Epidemiology Advisory Board)

Yvonne D'Arcy: Purdue (Ad board, Speakers Bureau—non-branded materials), Ortho-McNeil (Speaking—non-branded), Egalet (Ad board), Practicing Clinicians Exchange (Speaking—Chronic Pain)

Kelly K. Dineen: My spouse is a full-time employee of Medtronic, Inc., which manufactures medical devices, including implantable devices for the treatment of chronic pain. I did not write about the use of devices for pain.

Jeffrey Fudin: Astra Zeneca (Speakers Bureau); Collegium (Consultant, Films); Daiichi Sankyo (Advisory Board); DepoMed (Advisory Board, Speakers Bureau); Endo (Consultant, Speakers Bureau); Iroko Pharmaceuticals (Speakers Bureau); Kashiv Pharma (Advisory Board); KemPharm (Consultant); Pernix Therapeutics (Speaker); Remitigate, LCC (Owner)

Bill H. McCarberg: Advisor: Pfizer, Collegium, DepoMed, Daiichi Sankyo, Pernix, Eaglet; Stock holdings: Johnson and Johnson, Biospecifics Technologies, Nektar Therapeutics, Galena, Collegium; Speaker's Bureau: Collegium

John F. Peppin: Janssen (Consultant); Ferring Pharmaceuticals (Consultant, Speaker); OneSource Regulatory (Consultant); YourEncore (Consultant)

Anand C. Thakur: DepoMed Pharmaceuticals (Speaker); Purdue Pharmaceuticals (Speaker); Kaleo Pharmaceuticals (Speaker); BDSI Pharmaceuticals (Speaker); Daiichi-Sankyo Pharmaceuticals (Speaker)

PRESCRIPTION DRUG DIVERSION AND PAIN

PREFACE

Chronic pain and the use of prescription opioids: There are very few topics today that can raise more emotional response than this combination, which just happens to be the central theme of this book. In today's world, opioids, like some of the people who use them and some who prescribe them, are being vilified because of what experts are calling an *epidemic* of opioid abuse. Described as "painkillers" and "narcotics" by the media, there is a growing sense that physicians who routinely prescribe these drugs for nonmalignant chronic pain are compromising professional norms, including that of the sacred Hippocratic Oath directive *to first do no harm*.

Chronic pain patients, many of whom are already beset by their medical problems, are further troubled and confused by the back-and-forth public debates over the safety and soundness of their treatment protocols. The topic of opioids is more divisive today than ever before.[1] Ideology rather than physiology becomes all too often the prevailing sentiment not only for practitioners, but also for pain patients, policymakers, public health and safety officials, and even members of the public. Views are often expressed in divisive pronouncements rather than arrived at through civil discourse.

Opioids indeed are controversial, but the complete story of their benefits and burdens remains untold. From time to time, data may be selected and interpreted to buttress a claim that, in turn, may be untrue or only partially true. There has been so much written in the medical literature for so many years on this topic that one should have no problem finding an authoritative source or two to reference a pet theory. Although concern for the long term use of opioids has existed for millennia, the wave of current fear gripping the nation no doubt has come about because of the increasing morbidity and mortality associated with their use in treating nonmalignant chronic pain.

Over just the last several years, a major shift has occurred in the literature over the long term use of opioids to treat chronic pain. The effect of this shift has been felt by patients who suddenly find their healthcare providers reluctant to continue chronic opioid therapy.

In the absence of suitable alternatives, many patients will likely bear the personal burden of this changing environment. Some will become dispirited and confused by the stereotypical accounts of opioid addiction that abound in the popular media.[2]

As we show in this book, essential data about opioid abuse, morbidity, and mortality are lacking and what little data we have are derived from flawed and obsolete government databases. Yet, these sources are relied upon for public policy development, resource allocation, and lawmaking. In the absence of sound data, ingrained cultural feelings about addiction can become a powerful driver of attitudes, even among pain specialists who, despite their professional training and experience, may be influenced by such bias in their prescribing practices.

Most would agree that the modern era of chronic pain treatment began in earnest the mid-1990s with the introduction of an extended-release form of oxycodone called OxyContin®. It was aggressively marketed as the answer to millions of untreated or undertreated chronic pain patients. OxyContin offered benefits that shorter acting immediate-release opioids lacked. Professional medical groups and organizations representing the interests of pain patients heralded the new drug. With their support, in 2000, congress enacted a statute declaring the decade beginning in 2001 as the "Decade of Pain Control and Research."

Lurking beneath the growing euphoria at the time was a growing concern by state and federal officials over increasing reports of overdoses and deaths attributed to the misuse of OxyContin, particularly in places like Maine, Ohio, and parts of Appalachia. By the end of the Decade of Pain Control and Research, the government was geared up and ready to transition to a decade of drug control. In this book, we explain in detail when, how, and why this happened.

A basic aim of this book is to inform healthcare professionals and others about some of the essential aspects of chronic pain treatment, particularly in an time of changing attitudes about the long term use of opioid therapy. Opioids are not, and never have been, a panacea for treating pain; they are just one of several tools available for use in specific instances and with specific patients. Much has changed in the pain field since this book was first envisioned, and much is expected to change over the coming years.

It is the hope of the authors and publisher that readers employed in the fields of law enforcement, medicine, regulatory policy and enforcement, pharmacy, drug treatment, and academia, as well as interested members of the general public, will benefit from the expertise and candor of the authors. This volume cannot begin to cover all of the important issues surrounding prescription opioids and chronic pain; rather, it is meant to be a starting point, a roadmap of sorts for professionals and non-professionals interested in the modern era of pain treatment and how we arrived at where we are today.

As mentioned in the dedication page, the editors would like to offer their sincere condolences to the families of Drs. Kenneth L. Kirsh and Howard Smith, two dedicated and skilled individuals with whom we began this project and who untiringly worked for the betterment of pain patients.

John F. Peppin, John J. Coleman, and Kelly K. Dineen

REFERENCES

1. http://health.usnews.com/health-news/blogs/eat-run/2015/04/08/the-problem-with-opioids-for-chronic-pain. Accessed May 10, 2017.
2. Peppin JF. Marginalization of patients with chronic pain on chronic opioid therapy. *Pain Physician*. 2009;12:493–498.

PRESCRIPTION DRUG DIVERSION AND PAIN

CHAPTER 1

OPIOID MEDICATIONS

Old Wine in New Bottles

Timothy Atkinson, John J. Coleman, and Jeffrey Fudin

OPIOID HISTORY

An *opiate*, as defined by the United Nations Office of Drugs and Crime, is a substance naturally derived from the poppy plant, including raw opium, several psychoactive substances (thebaine, papaverine, and noscapine), morphine, codeine, and the semisynthetic heroin.[1] In contrast, the term *opioid* is broad and includes everything from the naturally occurring opiates (e.g., opium, morphine, codeine, etc.) to the synthetic or semisynthetic opioids used medically for the treatment of pain (e.g., fentanyl, hydrocodone, hydromorphone, methadone, oxycodone, oxymorphone).[1]

The appropriate use of opium and its derivatives and the distinction between their medical and recreational (or nonmedical) use are problems not unique to modern times. Booth (1996) reports that as early as 3400 BC opium poppies were cultivated in Mesopotamia by the Sumerians, who referred to it in their writings as the "joy plant."[2] The Ebers Papyrus (2000 BC) contains over 700 recipes using opium, while Assyrian medical tablets (700 to 601 BC) list opium in 42 of 115 vegetable remedies.[2] The prominent use of opium in spiritual life is evident as well and is clearly evident in the portrayal of many Greek and Roman gods wearing or holding opium poppies.[3] In the hands of priests, opium was a powerful agent to relieve grief, worry, and regret while producing a seemingly spiritual euphoria for the user.[2]

As demand for opium increased so did its influence on international trade and policy. For centuries, opium was traded as a commodity along the Silk Road from the Middle East, India, and China across the continent to Europe.[4] In the 17th century, in response to increasing opium demand in England, the East India Company was formed, and it dominated opium trade and production in Southeast Asia for nearly two centuries.[2] During

this time, Great Britain fought two "opium wars" with China for the continued right to import and sell opium in China.[5]

Medical use of opium has been a polarizing issue for centuries, with many physicians both praising and condemning its use. As early as the third century BC, Greek physicians Erasistratus and Diagoras opposed opium use.[2] Erasistratus promoted complete abstinence while Diagoras went even further, declaring it would be better to suffer pain than become dependent upon opium.[2] Galen, living in the first and second centuries AD, claimed that opium cured nearly every known ailment.[2] Galen also published findings on the toxic side effects of opium and, importantly, his writings show that he understood the concept of tolerance.[2] There were other physicians of the time who believed opium should be used sparingly and judiciously and only within controlled environments.[2] This was the position of Hippocrates (460–357 BC), the "father of medicine," who described opium as useful for the treatment of headaches, cough, asthma, pain, and melancholy.[2]

Thus, from the earliest times to the present, opium has played a significant role in medicine. At the end of the 19th century, Sir William Osler, first physician-in-chief of Johns Hopkins Hospital and one of four original faculty members at its medical school, referred to opium as "God's Own Medicine."[2] Despite these testimonials, concerns for opium's adverse side effects have always shared equal concern among practitioners. In 1940, speaking before the 91st annual session of the American Medical Association (AMA), noted surgeon Lyndon E. Lee, Jr., MD, cautioned members in the use of opioids, even for end-of-life care:

> The use of narcotics in the terminal cancer patient is to be condemned if it can possibly be avoided. Morphine and terminal cancer are in no way synonymous. Morphine usage is an unpleasant experience to the majority of human subjects because of undesirable side effects. Dominant in the list of these unfortunate effects is addiction.[6]

However, definitions of addiction have changed dramatically since Dr. Lee's time. The American Society of Addiction Medicine now defines addiction as follows:

> Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.[7]

Whether in the third century BC, 1940, or today, physicians have always had to weigh the therapeutic benefits of opium against its known risk of addiction and dependence.

US LEGISLATIVE HISTORY

The modern medical use of opium began in Germany in 1806 with the publication of experiments describing *Principium somniferum*, or morphine.[2] For the first half of the 19th century, physicians mainly administered opium to relieve pain, cough, or diarrhea.[2] Morphine was marketed as early as 1817 for analgesia and as a cure for alcohol and opium addiction.[2] The intravenous administration of morphine became possible in the 1850s with the invention of the hypodermic needle, and the rapid onset of action and ease of use quickly made intravenous morphine the analgesic gold standard for many healthcare professionals.[2,5]

The second half of the nineteenth century brought with it the highest rate of opiate use in American history. Numerous opium-containing concoctions were pitched for a wide variety of ailments, often promoted with exaggerated claims while failing to disclose their potentially toxic ingredients.[8] The American Civil War was the first major conflict in which morphine in powdered form was available and used as a battlefield analgesic.[9] Musto describes how medics, employing the new technology of the hypodermic syringe, unsparingly administered morphine to wounded soldiers, many of whom would bring their addiction home with them after the war.[9]

Following the Civil War, the use of opiates in so-called patent medicines sold by street peddlers, mail-order suppliers, and local druggists added to the problem of addiction.[8,10] Physicians of the time often overprescribed opiates for relatively simple ailments such as menstrual symptoms, children's colic, or infants' teething pain.[11] This practice, according to Kandall, contributed to middle-class white women becoming the largest group of addicted individuals.[11] By the 1890s, some were expressing concern about the rising levels of opiate addiction, and "inebriety hospitals," modeled on insane asylums, were opened with the intention of treating addiction as a medical problem.[4]

Early opiate addiction treatment consisted of experimental regimens that, in retrospect, were sometimes brutal and ineffective. Musto describes the "Towns Cure," named for Charles B. Towns, a wealthy stockbroker who despite his lack of formal medical training had a profound interest in "curing" opiate addiction. In 1909, Towns convinced a nationally prominent physician, Dr. Alexander Lambert (later president of the AMA), to endorse his treatment program. The Towns Cure consisted of denying addicts narcotics while aggressively treating their symptoms of withdrawal with strong laxatives and other drugs. This "cure" became the standard of care for the treatment of opiate addiction until the 1920s, when Lambert and others recognized the symptoms and significance of psychological dependence resulting from the use of narcotics, and the need to address the addict's drug cravings to achieve long-term remission.[9]

The popularity of the Towns Cure notwithstanding, the patent medicine industry wasted no time getting into the business of detoxification and opiate addiction treatment. Samuel Hopkins Adams, a noted investigative journalist for *Collier's Weekly*, wrote a series of articles called "The Great American Fraud" in which he exposed fraudulent claims by the patent medicine industry, including those by the "fakers claiming to cure the drug habit."[8] Adams purchased 16 different patent medicines being advertised as "cures" for morphinism

or opium addiction.[8] All 16 were found to contain morphine.[8] Describing the purveyors of these bogus cures, Adams wrote:

> At the bottom of the noisome pit of charlatanry crawl the drug habit specialists. They are the scavengers, delving amid the carrion of the fraudulent nostrum business for their profits. The human wrecks made by the opium and cocain [*sic*] laden secret patent medicines come to them for cure, and are wrung dry of the last drop of blood.[8]

Adams' writings were credited with raising public awareness of the problem of patent medicines that, in turn, influenced Congress to pass the Pure Food and Drug Act of 1906.[9,12] While this act did not prevent sales of dangerous drugs containing opiates and cocaine, it did require accurate labeling of all contents for medicinal products sold in interstate commerce.[9]

In 1898, the Bayer Company began marketing a cough suppressant featuring a new ingredient called "heroin."[5] Fewer obvious side effects led to the assumption that heroin was not addictive.[5] Heroin's effectiveness as a pain reliever and cough suppressant were soon overshadowed by its abuse potential. Heroin's increased potency over morphine, its availability over the counter or from street peddlers, and its ease of use made it a natural target for recreational drug abusers who crushed and snorted or solubilized and injected the drug.[4] By 1910, heroin abusers were mostly working-class young men.[4]

In 1909, the first international opium conference was held in Shanghai, China, to discuss worldwide control of opium.[13] While not reaching consensus on control, the meeting nonetheless raised international awareness of the problem of opiate addiction, particularly as it affected China.[13] In 1914, a second opium conference was held at The Hague, Netherlands, where participants agreed to reduce opium production and restrict nonmedical use of the drug.[2,13] US attendees, elected by their fellow members to preside over both conferences, were embarrassed by having to propose international controls that were not yet adopted by the United States.[2]

Public opinion in the United States supported a proposed federal law to regulate the sale of narcotic drugs.[14,15] With support from Congress and President Woodrow Wilson, the Harrison Narcotics Tax Act of 1914 was enacted into law.[16] This act provided "for the registration of, with collectors of internal revenue, and to impose a special tax on all persons who produce, import, manufacture, compound, deal in, dispense, sell, distribute, or give away opium of coca leaves, their salts, derivatives, or preparations, and for other purposes."[17] Oddly, the act treated coca leaves as a narcotic.[17] The act permitted "the sale, dispensing, or distributing of any of the aforesaid drugs by a dealer to a consumer under and in pursuance of a written prescription issued by a physician, dentist, or veterinary surgeon registered under this Act."[17] Thus, for the first time, narcotic drugs could be dispensed or sold only upon presentation of a valid prescription issued by a practitioner registered under the act.

Perhaps the most controversial aspect of the Harrison Act was a relatively short provision that in later years would prove to have enormous legal significance. Restrictions placed on regulated drugs, according to Section 2, Subparagraph (a), of the act, did not apply "To the dispensing or distribution of any of the aforesaid drugs to a patient by a physician, dentist, or veterinary surgeon registered under this Act *in the course of his professional practice only*"[17] [emphasis added].

Although the scandals involving the patent medicine industry may have raised public support for regulation of narcotics, the Harrison Act's real target was the prescribers and dispensers of medicinal narcotics, whom some viewed as purveyors of addiction.[18] In just the first 4 months following the passage of the act, federal authorities charged 257 physicians and 40 dentists with violating the law.[19] Included among them was Dr. Jin Fuey Moy of Pittsburgh, who was convicted of prescribing 1/16 of an ounce of morphine sulfate to Willie Martin, an addict.[19] Dr. Moy's conviction mobilized the medical community, and in 1915, his case was appealed to the US Supreme Court.[19] There, on June 5, 1916, by a vote of 7–2, the Justices sided with Dr. Moy and his supporters, ruling that it was unlawful for the government to interfere with what amounted to the lawful practice of medicine.[20,21]

In 1919, the Supreme Court revisited the Harrison Act by accepting two new drug cases. In the first, Dr. Charles T. Doremus of San Antonio was charged with providing 500 tablets of morphine to a known addict.[19] Although a district court had ruled that the federal law was unconstitutional because it usurped the police powers of the state, the Supreme Court disagreed and declared the Harrison Act constitutional.[22]

The second case involved W. S. Webb, MD, and a pharmacist named Jacob Goldbaum, both from Memphis.[19] They were charged with routinely supplying addicts with large quantities of morphine.[19] In upholding their convictions, the Supreme Court found that, contrary to the Harrison Act's requirement, Webb and Goldbaum were not acting in the course of their professional practice only.[19,23] In reversing its earlier decision in Dr. Moy's case, the Court held that a physician might not prescribe "for the purpose of providing the user with morphine sufficient to keep him comfortable by maintaining his customary use."[23]

While the Treasury Department's strategy for addressing the problem of addiction was to focus on errant physicians and pharmacists, some in Congress had a different view of addicts. Representative Stephen G. Porter of Pittsburgh, chairman of the House Committee on Foreign Affairs and a staunch supporter of strict drug control, viewed addiction as a disease: "A person who is addicted to drugs is sick. He or she is the victim of a disease and should be placed where treatment can be given. You can't cure a sick person by sending that person to jail."[24]

Convinced that the bogus "cures" offered by the patent medicine industry were doing more harm than good, in 1929 Congress enacted legislation proposed by Porter to establish two "narcotic farms" run by the US Public Health Service as prison-hospitals dedicated to finding a cure for drug addiction.[25] The Porter Narcotic Farm Act, as it was called, mandated that the care of those confined to the farms "shall be designed to rehabilitate them, restore them to health, and where necessary train them to be self-supporting and self-reliant."[25,26]

The first narcotic farm was opened in 1935 on 1,000 acres of farmland just outside of Lexington, Kentucky.[27] By all accounts, it was a novel approach to addiction research.[27] Male and female convicts arrested for drug offenses did time alongside volunteers who checked themselves in for rehabilitation.[27] The treatment regimen followed the then-standard approach to treating psychological disorders with discipline and compassion in a healthful, rural setting, where patients could receive vocational therapy and group or individual psychotherapy, attend religious services, participate in indoor and outdoor recreation, and perform physical labor by working on a real farm.[27] The media enjoyed covering the narcotic farm, alternating between describing it as "A New Deal for the Drug Addict" and "A Million Dollar Flophouse for Junkies."[27]

In 1938, the second farm was opened in Fort Worth, Texas.[27] For several decades these two prison-hospitals would be the only research centers in the world devoted solely to finding a cure—or at least effective treatment—for drug addiction.[27] Although they never succeeded in fully achieving this goal, the scientific research performed at these unique facilities eventually led to the first protocols using methadone drug therapy in the treatment of opiate addiction.[27] By 1949, methadone was the preferred medication for detoxification at the Lexington narcotic farm.[27] In the 1960s, Drs. Vincent Dole and Marie Nyswander of the Rockefeller Medical Research Institute were credited with pioneering the general use of methadone to treat opiate addiction.[28] Although it had been used as an experimental protocol since the late 1940s, the first statutory approval of "maintenance treatment" (referring to the use of methadone for opioid addiction treatment) occurred in the Narcotic Addict Treatment Act of 1974.[29]

In 1930, with the demise of the Bureau of Prohibition on the horizon, President Herbert Hoover established the Federal Bureau of Narcotics within the Department of the Treasury and appointed Harry J. Anslinger, a former Bureau of Prohibition agent and counselor officer with the Department of State, as its first commissioner.[30] Anslinger's responsibilities included representing the United States at the League of Nations' Opium Advisory Committee, where he quickly gained an international reputation for being tough on drug crimes.[13] With the end of World War II, the League of Nations was replaced by the United Nations (UN), and in 1946, the responsibilities of the former Opium Advisory Committee were transferred to a newly formed but similarly designed UN Commission on Narcotic Drugs. Anslinger maintained his position as a US representative to the commission.[13]

On the domestic front, Anslinger was a well-known public figure whose strong views on drug control and repertoire of exciting drug cases made him a popular after-dinner speaker and a frequent guest on radio and TV.[30] In a 1948 movie, *To the Ends of the Earth*, that dramatized the work of his agents, Anslinger appeared in a cameo role as himself to explain the importance of international drug control.[31] In 1951, Anslinger's public support helped Congress to pass the Boggs Act, which included the first mandatory minimum sentences for drug offenses.[4] Anslinger would continue to be an influential figure on the national and international drug scene until his retirement in 1962 at age 70.[19]

The Controlled Substances Act (CSA) of 1970 was passed in response to an alarming increase in drug abuse during the 1960s.[19] The CSA classified drugs in five "schedules" according to their medical usefulness and abuse potential. Responsibility for enforcing the CSA was assigned to the newly created Bureau of Narcotics and Dangerous Drugs, the successor agency to Anslinger's Federal Bureau of Narcotics, which was abolished by executive order in 1968.[32]

To carry out the provisions of the CSA, Congress gave the Attorney General and the Secretary of Health, Education, and Welfare statutory authority to assess the abuse potential of drugs and other substances. Five "schedules" or classification categories for controlled substances, including regulated pharmaceutical drugs, were established, and specific, detailed criteria addressing abuse potential, medical usefulness, and psychological and physiological dependence were included to differentiate substances for control purposes.[33]

Schedule I and II controlled substances, according to the CSA criteria, have "high potential for abuse" but differ as to their currently accepted medical use in treatment in the United States.[34] Schedule I substances lack accepted safety for use under medical supervision,

whereas Schedule II substances have "a currently accepted medical use in treatment in the U.S. or a currently accepted medical use with severe restrictions."[34] Substances in Schedules III, IV, and V are approved for medical use and have descending abuse potential.[34]

The CSA regulates approximately 1.6 million "registrants," comprising physicians, pharmacies, wholesale distributors, packagers, reverse distributors, manufacturers, teaching institutes, researchers, hospitals, and other handlers of controlled substances.[35] Rules are designed to ensure the security of the regulated drugs and to prevent diversion from legitimate to illegitimate channels.[36] Understandably, the rules are stricter and enforced more frequently when the substances in question pose a greater threat to public health and safety.[36] For example, the CSA expressly prohibits the refilling of Schedule II prescriptions.[37] In 2007, in response to numerous requests from prescribers and patients, the Drug Enforcement Administration (DEA) issued a Final Rule allowing "practitioners to provide individual patients with multiple prescriptions, to be filled sequentially, for the same schedule II controlled substance, with such multiple prescriptions having the combined effect of allowing a patient to receive up to a 90-day supply of that controlled substance."[38] The rule contained a number of additional requirements that must be met by the prescriber.[38] The easing of the statutory prohibition on refilling Schedule II prescriptions was hailed by patients and practitioners; of the 264 public comments received in response to DEA's proposed rule, 88.5% (231) were in favor of the change.[38]

Under the CSA, prescription refills for substances in Schedules III and IV may be authorized five times for up to 6 months and they may be transmitted to the dispensing pharmacy by phone, facsimile, or electronic prescribing.[39] State controlled substance laws may differ from federal ones in the sense that they may be stricter, but never less severe. For example, hydrocodone-containing products were designated under state law as Schedule II controlled substances in New York more than a year before the federal law was amended in October 2014 to reclassify all hydrocodone products to Schedule II.[40,41]

OPIOID-RELATED MORBIDITY AND MORTALITY

According to the Centers for Disease Control and Prevention (CDC), Opioids—prescription and illicit—are the main driver of drug overdose deaths.[42] Opioids were involved in 33,091 deaths in 2015, and opioid overdoses have quadrupled since 1999.[43] Between 2013 and 2014, the age-adjusted rate of death involving methadone remained unchanged; however, the age-adjusted rate of death involving natural and semisynthetic opioid pain relievers, heroin, and synthetic opioids other than methadone (e.g., fentanyl), increased 9%, 26%, and 80%, respectively.[44] The sharp increase in deaths involving synthetic opioids other than methadone, in 2014 coincided with law enforcement reports of increased availability of illicitly manufactured fentanyl, a synthetic opioid; however, illicitly manufactured fentanyl generally is not distinguished from prescription fentanyl in death certificate data.[44]

The CDC's data for drug-related deaths are based on a review of death certificates completed by funeral directors, physicians, medical examiners, and coroners.[45] Studies of

these data have revealed several limitations, not the least of which is the ambiguity often found in death certificates filed before postmortem toxicology tests are completed.[46] A certificate in which the attending authority writes "suspected drug overdose" or "drug overdose" as the cause of death lacks specificity as to the drug(s) that caused or contributed to the death.[46] It is estimated that one in four drug-related deaths cannot be categorized according to the specific drugs involved because of this limitation.[46] Thus, it is likely that the totals given by the CDC for annual drug-related deaths attributed to opioids or to any other specific class of substances represent an undercount.[47]

Patients taking opioids may accidentally die of drug interactions.[48] In approximately 29% of opioid-related deaths, victims were found to have consumed benzodiazepines, which can heighten central nervous system depression when combined with opioids, thus resulting in reduced respiratory drive—something that can prove fatal in some patients.[49] Other medication classes that are present in higher numbers in opioid-related deaths include antidepressants (13.4%), antiepileptic and antiparkinsonian drugs (6.8%), and antipsychotic and neuroleptic agents (4.7%).[49]

Methadone accounts for only 2% of prescriptions for opioids but consistently results in over 30% of opioid-overdose deaths, more than twice the amount of any other opioid.[50] There were nearly six times as many methadone overdose deaths in 2010 as there were in 1999, mostly driven by an increase in the number of prescriptions written for pain.[51] While methadone's multiple mechanisms of action can be useful in the treatment of chronic pain, it often is prescribed by practitioners unfamiliar with its complicated features—including its variable and extensive distribution into tissues, its long half-life, QTc prolongation that may result in dangerous cardiac arrhythmias, variations in dose conversions, and a myriad of potential drug interactions that can increase methadone's absorption to dangerous levels.[52–54] Recent reports point to an underappreciated but clinically significant interaction with P-glycoprotein that may contribute to fatal overdoses resulting from medications that are generally considered safe to administer with methadone.[55]

Methadone is the preferred option by many insurers based solely on cost and is prescribed frequently by primary care physicians for headaches (17%), although efficacy is lacking for this indication.[51] More alarming is the fact the CDC's finding that nearly a third of methadone prescriptions were dispensed to patients who had received no opioids at all in the prior 30 days.[51]

PAIN COMMUNITY

The number of patients being treated for various chronic pain conditions, including cancer survivors and patients with lower back pain, has increased significantly over the last 15 years.[56] At the same time, the number of prescriptions for opioids has dramatically increased, as has their misuse.[57] According to a government survey of persons 12 years or older who admitted to using pain relievers nonmedically in 2011, 54.2% reported that they obtained their most recently used drug from a family member or friend for free, 18.1% said they obtained the drug from one doctor, and 3.9% said they obtained the drug from a street dealer or stranger.[58] In a follow-up question asking where the respondents believed that

their family member or friend obtained the drug, approximately 81% believed that the relative or friend obtained the drug from just one doctor.[58]

Opioids diverted for nonmedical purposes come primarily from prescriptions issued by individual practitioners, usually primary care physicians.[58] However, there is evidence that thefts from hospital and pharmacy drug supplies, as well as in-transit thefts from manufacturers and distributors, may also be a significant source of diverted opioids.[59] As previously mentioned, at least one government survey found that friends and family members represent the single greatest source of abused pain medications.[58] Since 2006, national strategies to reduce prescription drug abuse have called for educating patients and their families as to the importance of quickly and safely disposing of unneeded medications.[60] In addition, since 2010, state and federal law enforcement agencies have collaborated on collecting unused or outdated prescription drugs from the public.[61] According to the DEA, the National Prescription Drug Take-Back Day collection by state and federal law enforcement agencies at 5,500 sites across the nation in April 2017 resulted in the removal of a record 900,386 pounds of unwanted medicines.[61]

WHY PRESCRIPTIONS FOR OPIOIDS HAVE INCREASED

In 1998, the Federation of State Medical Boards of the United States released Model Guidelines for the Use of Controlled Substances for the Treatment of Pain; these guidelines were revised and expanded in 2004.[62] They urged state medical boards to encourage physicians to view the undertreatment of pain as inappropriate care and provided guidance for performing a patient evaluation, preparing a treatment plan, obtaining a patient's informed consent, preparing and executing an agreement with the patient covering the proposed treatment, and conducting a periodic review of the patient's case.[63] The guidelines also provided assurance of support to pain physicians prescribing controlled substances for a legitimate medical purpose, provided the physician maintains proper and complete medical records.[63] State medical boards were also encouraged to cooperate with state attorneys general to evaluate state rules and regulations to identify regulatory restrictions that might impede the use of opioids in pain management.[63]

Following widespread acceptance and implementation by state medical boards, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) approved new standards for pain management in 2000.[64] Because JCAHO (in 2007 the group shortened its name to the Joint Commission) is the accrediting body for hospitals and long-term care and behavioral health facilities, these institutions were expected to adopt the new standards for treating pain or risk losing their accreditation.[65]

Not surprisingly, the increased awareness of untreated pain over the course of the last several decades was accompanied by an increase in the number of prescriptions for pain relievers.[66] The US Food and Drug Administration (FDA) reports that the number of outpatient opioid prescriptions dispensed from US retail pharmacies increased from 174.1 million in 2000 to 256.9 million in 2009, a 67.7% increase.[67] On an average day in the United States, the Department of Health and Human Services reports, more than 650,000 opioid